PEDIATRIC CLINICS OF NORTH AMERICA

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CONTENTS

SYMPOSIUM ON RESPIRATORY DISORDERS

Foreword	*Waldo E. Nelson, M.D.*	1
Blood Chemical Deviations in Respiratory Disorders of the Immediate Postnatal Period	*Helen S. Reardon, M.D.*	3
Clinical Evaluation of Respiratory Function in Newborn Infants	*Herbert C. Miller, M.D.*	17
Roentgen Diagnosis of Pulmonary Disease of the Newborn Infant	*Guido Currarino, M.D.* *Frederic N. Silverman, M.D.*	27
Respiratory Disorders of Newborn Infants: Correlation of Clinical and Pathological Observations	*Harriet M. Arey, M.D.* *James B. Arey, M.D.*	53
Bacterial Pathogens of the Respiratory Tract of the Newborn Infant	*Margaret H. D. Smith, M.D.*	69
Anomalies of the Respiratory Tract	*Benjamin H. Landing, M.D.*	73
Unidentified Nonbacterial Infections of the Nasopharynx: The Common Cold	*Eli Gold, M.D.* *Frederick C. Robbins, M.D.*	103
Nonbacterial Infections Affecting the Nasopharynx	*Robert H. Parrott, M.D.* *Henry G. Cramblett, M.D.*	115
Bacterial Infections of the Nasopharynx: With Particular Reference to the Prevention of Rheumatic Fever and Glomerulonephritis	*Willard C. Schmidt, M.D.* *Charles H. Rammelkamp, Jr., M.D.*	139

Symptomatic Relief of Nasopharyngeal Infections in Infants and Children: The Use and Misuse of Antibiotics, Nose Drops, Ear Drops, Cough Medications and Antihistaminic Drugs	*Harry C. Shirkey, M.D.*	155
Acute Inflammatory Disorders of the Larynx and Laryngotracheal Area	*Edward F. Rabe, M.D.*	169
Bronchiolitis (Acute Asthmatic Bronchitis, Acute Capillary Bronchitis)	*Robert H. High, M.D.*	183
The Relationship of Canine Distemper to Human Respiratory Disease	*John M. Adams, M.D.* *David T. Imagawa, Ph.D.*	193
Interstitial Plasma Cell Pneumonia	*E. K. Ahvenainen, M.D.*	203
Staphylococcal Pneumonia and Empyema	*Gilbert B. Forbes, M.D.* *George L. Emerson, M.D.*	215
Bronchopulmonary Suppurative Disease: Differential Diagnosis and Management	*Nancy Huang, M.D.*	231
Hydrocarbon Pneumonitis	*C. William Daeschner, Jr., M.D.* *Russell J. Blattner, M.D.* *Vincent P. Collins, M.D.*	243
Pulmonary Tuberculosis: The Primary Lesion (Specific vs. Nonspecific Therapy)	*Arthur Robinson, M.D.*	255
Pertussis: Current Status of Prevention and Treatment	*Harriet M. Felton, M.D.*	271
Allergic Problems in the Upper Respiratory Tract, Including the Ear	*Victor C. Vaughan, III, M.D.*	285
Asthma: Management of the Acute Attack and of the Chronic Disease	*Jerome Glaser, M.D.*	293
Index		313

FOREWORD

WALDO E. NELSON, M.D.

Consulting Editor

It is timely to assemble the facts and theories relating to the respiratory function of infants and small children. Within the areas of this physiological activity lie the keys to understanding—pathogenetically, clinically and pathologically—of the principal causes of morbidity in the first few years of life.

Within comparatively recent years the combination of available effective antibacterial agents, the improved prophylactic care for the newborn infant and the better socio-economic situation available to the pregnant woman and her offspring have reduced morbidity and mortality rates among this dependent age group to levels some have enthusiastically considered to be approaching irreducible minimums. To the more realistic observer, opportunities for a clearer delineation of remaining problems stand out with increasing clarity. Further, he notes with concern the emergence of new and, in some instances, iatrogenically contrived disturbances, as evidenced by the capacity of the staphylococcus and certain gram-negative bacilli to adapt themselves to antibiotically invested environments and by the permanent damage to the premature infant who is maintained in atmospheres with a high concentration of oxygen.

In the immediate newborn period we continue to be confounded clinically in respect to the significance of deviations in respiratory patterns. Often we cannot be certain of the nature of the underlying disturbance, or whether its origin is cerebral, pulmonary, metabolic or cardiovascular. But strides in these directions are being made. As of the moment the most significant contributions have emanated from the few physiologists and pathologists who have directed their inquiries to the problems of the newborn infant. Coordination of the activities of in-

vestigators in these fields with those of clinicians who are determined to find the true significance of clinical respiratory disturbances provides the only possible means for the solution of currently unanswered problems.

In the field of infectious disturbances we are, on the one hand, mainly dependent upon the microbiologist and the microbiologic chemist to keep ahead of and eventually to defeat the microbial invaders. But there must be more effective and more realistic assistance from the clinician. He must be aware that the indiscriminate use of antimicrobial agents carries the inherent danger that many of the organisms which he hopes to conquer may be able to adapt themselves not only to compete successfully with such agents, but even to live profitably in an environment containing them.

The opportunity to assemble this symposium designed to be interpretative of the more important respiratory problems which occur in the first few years of life has been a welcome privilege. It should be understood, however, that these contributions are in the strictest sense monographs and as such are the sole responsibility of the various authors. I have not assumed the right of editorial revision or addition, which, for example, I feel is essential in the construction of a textbook. I commend them with confidence that you will enjoy and profit from them as I have done.

BLOOD CHEMICAL DEVIATIONS IN RESPIRATORY DISORDERS OF THE IMMEDIATE POSTNATAL PERIOD

HELEN S. REARDON, M.D.

Respiration involves three separate though related processes: (1) external or pulmonary respiration, which makes possible the uptake of oxygen and elimination of carbon dioxide, (2) the transport of oxygen and carbon dioxide between the lungs and tissues, and (3) internal respiration, or the utilization of oxygen and excretion of carbon dioxide by the tissue cells.

The function of the lung is to maintain the proper tensions of the respiratory gases in the arterial blood. The processes involved in this function are those of ventilation of the lungs, diffusion of gases across the alveolar capillary membrane, the diffusion of gases to and from the red cells, and the maintenance of an adequate volume of capillary blood flow distributed evenly to all the ventilated alveoli (ventilation/blood flow).[1] These functions are accomplished by work of the respiratory muscles and circulatory system (right ventricle). The mechanism which activates and coordinates the respiratory muscles is called the respiratory center, a functionally integrated group of nerve cells located in the pons and medulla. The respiratory center not only sends impulses to the proper muscles at the correct time, but also adjusts the rate and depth of respiration for variations in oxygen requirement or carbon dioxide elimination. It is able to do this because of (1) an automatic rhythm which is modified by nervous and chemical factors, (2) gradations in sensitivity in respect to chemical stimuli, and (3) reciprocal innervation between inspiratory and expiratory centers.

From St. Christopher's Hospital for Children and the Department of Pediatrics, Temple University School of Medicine, Philadelphia.

CHEMICAL FACTORS IN RESPIRATION

The three chemical factors characteristic of metabolic activity are increased carbon dioxide tension (pCO_2), increased hydrogen ion concentration (decreased pH) and decreased oxygen tension (pO_2). They adjust the activity of the respiratory center to the metabolic needs of the body. Although not all these chemical stimuli act directly on the respiratory center, any one of them can cause a change in pulmonary ventilation.

Increased Carbon Dioxide Tension

Carbon dioxide gas is the primary chemical stimulus to the respiratory center, and is believed to be responsible for the regulation of respiration under ordinary circumstances. Very small changes in the pCO_2 of the alveoli or of the arterial blood will change pulmonary ventilation. For example, an increase of 1.5 mm. of carbon dioxide gas in alveolar air will double the respiratory minute volume. The mode of action is as follows:

The pCO_2 of alveolar air is in equilibrium with arterial pCO_2, so that an increase in alveolar pCO_2 is reflected by an increase of pCO_2 in arterial blood. The pCO_2 of arterial blood supplying the respiratory center determines the number of molecules of carbon dioxide in the cells of the respiratory center. Thus an increase of arterial pCO_2 will cause an increase in the pCO_2 of the cells of the respiratory center. The carbon dioxide content of the cells of the respiratory center determines the activity of the center. An increase in pCO_2 of the center will stimulate rate and depth of respirations. This is accomplished by (1) increasing the number of discharges of impulses to respiratory muscles, (2) increasing the number of participating neurons, and (3) increasing the number of muscles involved in the respiratory effort.

The clinical effect of this increased respiratory effort is *hyperventilation*. Hyperventilation causes a decrease in pCO_2 of the alveoli, the blood and the respiratory center in that order. When the pCO_2 of the cells of the respiratory center has returned to normal, regular activity of the respiratory center is resumed. Thus small elevation of the pCO_2 serves as an excitant of the respiratory center. Conversely, high elevation of carbon dioxide tension has a nonspecific depressant effect on the respiratory center, a fact which has been utilized in surgical anesthesia.

Increased Hydrogen Ion Concentration

Changes in hydrogen ion concentration of arterial blood may excite or depress the respiratory center indirectly by increasing or decreasing the plasma pCO_2. For example, when acid is added to the blood, it is neutralized by base released from its combination with bicarbonate, and the bicarbonate is released as carbon dioxide gas, increasing the partial pressure of carbon dioxide. The respiratory center is thus stimulated and increases pulmonary ventilation so that the excess carbon dioxide is eliminated from the lungs. If alkali instead of acid is added to the blood, carbon dioxide gas in the blood is lowered and diffuses from the cells of the respiratory center into arterial blood until equili-

brium is established. Thus the stimuli from the respiratory center to muscles become weaker, and pulmonary ventilation is decreased. The reduced pulmonary ventilation results in an accumulation of carbon dioxide in the alveoli, arterial blood and respiratory center. When the pCO_2 of the respiratory center returns to normal, regular respiration is resumed. These events take place only if the sensitivity of the medullary respiratory center is normal, the nervous connections intact, the respiratory muscles are functional and the lung is not diseased.

Severe changes in hydrogen ion concentration of arterial blood also set up reflexes in the carotid and aortic bodies which indirectly stimulate the respiratory center. Kety[6] correlated respiratory minute volume with plasma pH and found a sharp increase in minute volume between pH of 7.20 and pH 7.00. With further increase in acidity the ventilation decreases. Probably both central and reflex chemoreceptor mechanisms are involved in this process.

Decreased Oxygen Tension

A decrease in partial pressure of oxygen gas (pO_2) in arterial blood stimulates ventilation, but the response is much more variable and much less intense than the hyperpnea associated with increased pCO_2. Many persons do not show hyperpnea until the oxygen concentration of inspired air has fallen to 12 per cent or less; or, in terms of blood pO_2, a diminution of arterial oxygen tension to 67 mm. of mercury (normal, 90 mm.) is required before hyperpnea ensues. Thus anoxia is not a factor in maintaining respiratory activity under normal circumstances. A decreased blood pO_2 does not stimulate the respiratory centers directly, but rather produces hyperpnea by means of one of the respiratory reflex mechanisms of the chemoreceptor reflexes. The chemoreceptors are chemically sensitive nerve structures located in the carotid and aortic bodies. The respiratory reflexes arising in the aortic area are carried to the respiratory center by depressor nerves, and those arising in the carotids by sinus nerves.

The respiratory reflexes originating in each of these zones consist of two sets: (1) those governed by blood pressure and (2) those by chemical influences. The effect of impulses arising from the pressure receptors is inhibitory to respiration, but stimulation of the nerves from the chemoreceptors is excitant. Oxygen lack and lowered pH are the predominant chemical stimuli which motivate the chemoreceptor reflexes.

Summary

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Summary

In summary, plasma carbon dioxide gas is responsible for the regulation of respiration under normal circumstances by direct action on the

respiratory center in the brain. Reflexes initiated in the aortic and carotid bodies by decreased arterial oxygen tension or decreased pH may stimulate the respiratory center under unusual circumstances (severe asphyxia or acidosis).

TRANSPORT OF RESPIRATORY GASES

Hemoglobin is responsible for the transport of practically all the oxygen carried by the blood. A small quantity of oxygen is carried in the blood in physical solution as O_2, but the greater part is combined with hemoglobin as HbO_2. The amount of dissolved oxygen is directly proportional to the partial pressure of oxygen (pO_2) of the plasma; this is a straight-line relationship. Although the amount of oxygen combined with hemoglobin also depends on the pO_2 of the plasma, it is not a linear relationship, but an **S**-shaped curve. The advantages of the latter are: (1) pO_2 can decrease appreciably without changing the oxygen saturation of the blood so that the tissues will not suffer from anoxia, and (2) hemoglobin, when exposed to a low tissue tension of oxygen, will readily give up oxygen for utilization by the tissues.

Other variables which influence the ability of hemoglobin to combine with oxygen are (1) changes in hydrogen ion concentration or increased pCO_2, (2) changes in type of hemoglobin (fetal versus adult), and (3) body temperature.

If the acidity of the blood is increased, the amount of oxygen with which hemoglobin can combine at a given oxygen tension is decreased. The opposite is true with decreased acidity or loss of pCO_2. Fetal hemoglobin, which represents part of the total hemoglobin of the newborn infant, has the characteristic of increased affinity for oxygen at low oxygen tensions (just the opposite of the effect of increased acidity). Lowering of the body temperature will produce the same effect. Fetal hemoglobin, however, gives up oxygen to the tissues less readily than does adult hemoglobin.

The amount of carbon dioxide which can be carried in the blood varies directly with the partial pressure of carbon dioxide (pCO_2) to which the blood is exposed and inversely with the oxygen tension (pO_2). Carbon dioxide is transported from the tissues to the lung in the following way: 70 per cent as bicarbonate, of which one third is carried within the red cells and two thirds in the plasma; (2) 20 per cent as carbamino-bound carbon dioxide; and (3) 10 per cent in physical solution in the plasma. The acidity of the blood is disturbed very little by the constant production of carbon dioxide in the tissues, because most of the carbon dioxide is in chemical combination. About 13,000 mEq. per liter of carbon dioxide are excreted by the lungs of adults each day. If this were carried only as dissolved carbon dioxide,

$CO_2 + H_2O \leftrightharpoons H_2CO_3$, it would markedly increase the hydrogen ion concentration even though H_2CO_3 is a weak acid. Thus the hydrogen ion concentration, or its negative exponent, pH of the blood, is determined by the proportion of bicarbonate $[BHCO_3]$ to $[CO_2]$. In other words, this is one of, and the most important of, the blood buffer systems. A "buffer" system has the property of taking up H^+ or OH^- ions and thus acts to stabilize the pH of the blood. As long as the proportion of $[BHCO_3]$ to $[H_2CO_3]$ is 20:1, the pH will remain constant. The Henderson-Hasselbalch equation states that

$$pH = pK' + \log \frac{[BHCO_3]}{[H_2CO_3]}$$

$$pH = 6.1 + \log \frac{25.4 \text{ mM } CO_2/\text{Liter}}{1.27 \text{ mM } CO_2/\text{Liter}}$$

$$= 6.1 + \log 20$$

$$= 6.1 + 1.30 = 7.40$$

Since the amount of carbon dioxide carried in the blood varies directly with the tension of carbon dioxide (pCO_2), it follows that increases in pCO_2 will increase the dissolved carbon dioxide in the blood (H_2CO_3) and cause an acidosis. For example, if, during hypoventilation, the alveolar pCO_2 increased sufficiently to change the dissolved carbon dioxide from 1.27 to 1.6 mM. per liter, the pH would change from 7.40 to 7.30. However, in ordinary circumstances some of the dissolved carbon dioxide will quickly combine with base to form $BHCO_3$, the base being obtained from protein or one of the other blood buffer systems, and the proportion of $[BHCO_3]$ to $[H_2CO_3]$ will be increased. The amount of available base is limited, so that the new proportion of $[BHCO_3]$ to $[H_2CO_3]$ would be about 17:1 instead of 16:1. Therefore the pH will be about 7.34 instead of 7.30. If hypoventilation continues over a long time, renal conservation of base will aid in making base available for neutralization of carbon dioxide gas $[H_2CO_3]$.

If acid, other than carbonic acid, is added to the blood, $[BHCO_3]$ is reduced and $[H_2CO_3]$ is temporarily increased. The pCO_2 will initially increase and then decrease with hyperventilation so that less $[H_2CO_3]$ is present in the blood. If pulmonary compensation were perfect, i.e., if the alveolar pCO_2 were reduced sufficiently to cause a decrease of equal proportion of $[H_2CO_3]$ to $[BHCO_3]$, the 20:1 ratio would remain constant and the pH would be unaltered, even though the amounts of $[BHCO_3]$ and $[H_2CO_3]$ were decreased.

Usually there are two mechanisms by which the body defends itself against increased acidity. These are changes in pulmonary ventilation and the renal conservation of base. The renal mechanisms which aid in the conservation of base take longer to activate than that required by the pulmonary system to reduce carbon dioxide, so that acute changes are managed by pulmonary ventilation and chronic changes in acidity

or alkalinity are aided by the renal mechanism. The total carbon dioxide content ($H_2CO_3 + BHCO_3$) of the plasma is determined in the chemical laboratory, with simultaneous measurements of plasma pH. By calculation with the Henderson-Hasselbalch equation, or use of one of the nomograms, the individual components, $[BHCO_3] + [H_2CO_3]$, can be calculated. Thus in the examples just presented, (1) an increase of carbon dioxide content and (2) a decrease in carbon dioxide content of arterial blood were associated with a lowered pH (acidosis). These physicochemical variations are designated respectively as primary carbon dioxide excess, or respiratory acidosis, and primary alkali (base) deficit, or metabolic acidosis. The same type of reasoning may be applied to primary alkali excess (metabolic alkalosis) and primary carbon dioxide deficit (respiratory alkalosis), both of which produce an increase in plasma pH above the normal range.

The clinical pulmonary manifestation of the two types of acidosis and of alkalosis differ, as would be expected. *Respiratory acidosis* is the result of hypoventilation or uneven ventilation in respect to blood flow of the lung. The causes may be (1) depression of activity of the respiratory center by some drug (e.g., morphine) or (2) abnormality in the exchange of gases in the lung. If the respiratory center is depressed, respirations may be shallow and slow, but with primary difficulty of the lung, respirations may be rapid. With *metabolic acidosis* there is no primary abnormality in the ability of the lungs to ventilate; actually, increases in depth and in rate of respiration (hyperventilation) are compensatory features which prevent the blood pH from severe alterations.

With *metabolic alkalosis* respirations are shallow and slow because of the effort of the respiratory center to maintain an increased plasma $[H_2CO_3]$ in order to compensate for increased $BHCO_3$. With *respiratory alkalosis* respirations are deep and rapid, owing to the fact that the carbon dioxide deficit usually occurs as the result of stimulation of the respiratory center by something other than the pCO_2 level of the arterial blood. Anoxemia, high body temperature or various types of drugs (salicylates) will excite the medullary center sufficiently to cause lowered alveolar and thus blood pCO_2 and $[H_2CO_3]$.

TISSUE RESPIRATION

The subject of tissue metabolism is too involved to be reviewed in this article. However, a few general points in regard to *cerebral metabolism* should be considered.

Carbon dioxide is the most important gas in the regulation of respiration and the maintenance of a normal pH. However, tissue respiration deals almost exclusively with the supply and utilization of oxygen,

and carbon dioxide is of little importance in this respect. An increase in carbon dioxide can narcotize the body tissues, but does not destroy them directly as will oxygen lack. Indirectly, carbon dioxide may cause devastating changes in hydrogen ion concentration of the tissues.

The tissue oxygen supply depends not only on the amount of oxygen carried in blood, but also on the volume flow of blood to the tissues. For example, Kety[6] has shown that with moderate degrees of anoxia (10 per cent oxygen inhalation) the cerebral oxygen consumption is normal. This is attributed to compensatory efforts by the cardiovascular system which increase the heart rate and cause vasodilatation and increased cerebral blood flow. However, by lowering the blood glucose, oxygen consumption of tissue of the brain can be reduced. The cellular function of the brain and presumably that of the respiratory center depend upon a constant supply of blood glucose in addition to oxygen for normal cellular metabolism and differ from other tissues in that the reserve glycogen content of brain is relatively low.

Thus in an evaluation of respiratory disorders the ability of the tissues to utilize oxygen as modified by other blood chemical factors must be considered.

CHEMICAL REGULATION OF RESPIRATION IN THE IMMEDIATE NEONATAL PERIOD

At the time of birth full term infants delivered by the vaginal route have a slightly increased plasma carbon dioxide tension (pCO_2), a lowered oxygen saturation and a decreased plasma pH in their umbilical blood (Table 1).

TABLE 1. *Average Chemical Values for Umbilical Blood Obtained from Infants Delivered by Vaginal Route*

	ARTERY	VEIN
pCO_2 mm. Hg	51	44
pH	7.27	7.32
O_2 saturation %	32	67

These figures represent the chemical values in blood going to and returning from the fetus. They are not representative of the chemical values of blood going to a given area of the fetus—for example, the respiratory center—because of cardiovascular shunts which cause an admixture of arterial and venous blood. It may be assumed, therefore, that the respiratory center is bathed by blood which has a value for pH, pCO_2 and oxygen saturation between the values noted in the table for umbilical vein and artery blood.

Whether all three blood chemical stimuli aid in the initial stimulation to respiration is not known. The decrease in pH is not of the magnitude ordinarily considered necessary for stimulation of the chemoreceptor reflex mechanism. The slight increase in pCO_2 (a value between 51 and 44 mm. of mercury) should be adequate to stimulate the respiratory center, provided it is of normal sensitivity. Likewise, calculations of oxygen tension (pO_2) from measurements of oxygen saturation indicate that the lowered pO_2 is well within the range required for stimulation of respiration.[4]

Figures 1 and 2 and Table 2 illustrate the chemical changes of arterial blood that occur in the first four days of life.[8] Within one hour after

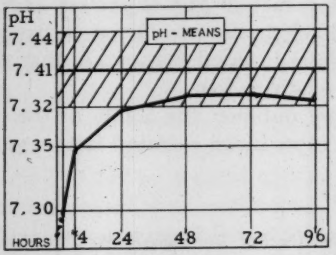

Fig. 1.

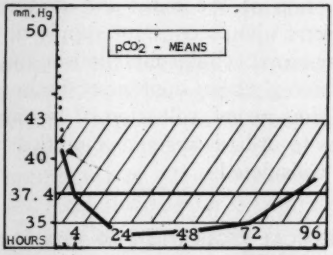

Fig. 2.

Fig. 1. Values for plasma pH in umbilical artery blood (dotted line) and temporal artery blood of full term infants at one, 4, 24, 48, 72 and 96 hours of life (solid line). The cross hatch represents range of values for normal adult males.

Fig. 2. Calculated values for plasma pCO_2 in umbilical artery blood (dotted line) and temporal artery blood of full term infants at one, 4, 24, 48, 72 and 96 hours of age (solid line). The cross hatch and horizontal line represent the range and average values for pCO_2 obtained in normal adult males.

birth the plasma pCO_2 is within the normal adult range, the plasma pH has not changed appreciably, but the base bicarbonate is reduced. Some time between four and 24 hours of age the plasma pH has increased to the normal adult range. This has apparently been accomplished by a decrease in plasma pCO_2 below the range considered necessary for stimulation of the respiratory center. From 24 hours through 72 hours the chemical findings remain unchanged, but by about 96 hours of age the plasma pH, $[BHCO_3]$ and pCO_2 are all approaching their normal ranges. The clinical evidence of hyperventilation is manifested by a slightly increased respiratory rate (26 to 48 per minute). During this time the oxygen saturation of the blood is close to or within the normal adult range. It is fairly obvious from these data that the body has lowered the pCO_2 in an effort to maintain a relatively constant pH.

Premature infants differ from full term infants in that the majority

of them (67 per cent) have an uncompensated metabolic acidosis manifested by slight decreases of the pH and of the base bicarbonate level, but by a normal pCO_2 after the first day of life.[10] About 10 per cent have a mild respiratory acidosis, and about 7 per cent have a respiratory alkalosis, with only 13 per cent having the usual adult values for plasma pH, base bicarbonate and pCO_2.

There are two reasons for the decreased plasma pH: (1) premature infants have the same basic defect noted in full term infants, i.e., a low [$BHCO_3$]; and (2) the infants are not able to compensate for the reduced [$BHCO_3$] by lowering the pCO_2 as do full term infants during the first three or four days of life. This may be due to (*a*) an inability of the premature infant to hyperventilate, owing to a relatively large

TABLE 2. *Average Values for Oxygen and Hematocrit in Temporal Artery Blood Obtained from Full Term Infants during First 4 Days of Life*

	HOURS					
	1	4	24	48	72	96
Oxygen content (volumes per cent)	21	24	22	22	22	21
Oxygen capacity (volumes per cent)	23	25	23	23	23	23
Oxygen saturation (per cent)	91	93	94	95	96	95
Hematocrit	55	60	55	53	51	53

residual pulmonary dead space or some other pulmonary difficulty or (*b*) to decreased sensitivity of the respiratory center to small changes in pCO_2.

Healthy premature infants and some full term infants do have a respiratory disorder characterized by a rhythmically irregular type of respiration of the Cheyne-Stokes type. Although the measured oxygen saturation of the blood is within the range of the average adult, this periodic respiratory pattern of premature infants can usually be converted to a normal adult type of respiration by the administration of oxygen.[15]

These observations suggest that healthy premature infants have an oxygen lack. This may be the result of a decreased supply of oxygen to, or utilization of it by, the tissues. Since the arterial oxygen saturation is adequate,[11] the respiratory pattern cannot be attributed to an inability of hemoglobin to carry oxygen.

Because of the apparent lack of oxygen in premature infants and possibly of an increase in plasma organic acids, Wilson et al.[15] have suggested that a partial anaerobic metabolism (in which glycogen is converted to lactate without utilizing oxygen) may exist for an indefinite time after birth, thus reducing the oxygen requirements.

Certainly the fetus or newborn infant may survive periods of anoxemia at the time of birth that would kill adults.

Alterations produced by anoxemia in human fetal tissue in vitro and newborn rats in vivo have been studied by Villee,[13] who suggests that the fetus may owe its ability to survive relatively long periods of anoxia during the birth process to energy derived from glycolysis, which is favored by the relatively high glycogen content of its tissues. He has shown that rat livers have a high content of glycogen just before delivery, but directly after birth the amount has been markedly decreased. Similar observations have been made on human fetal liver. Moreover, if newborn rats are placed in oxygen, the glycogen content of the liver and the blood glucose is much higher than in rats placed in an atmosphere without added oxygen. In the latter the glycogen content of the liver decreases; blood glucose falls, carbon dioxide gas decreases, the production of pyruvate increases, but neither pyruvate nor lactate accumulates. Villee[14] suggests that some intermediary metabolite other than lactic acid accumulates from which energy is derived.

It is apparent from this brief summary that further investigative work is necessary before the oxygen requirement of the tissues of newborn infants can be defined.

CHEMICAL DEVIATIONS

Increased pCO_2 and Hypoxia

Any disturbance in the newborn infant which results in *hypoventilation* will cause an increase in plasma pCO_2 and anoxemia, e.g., depression of the respiratory center by anesthesia, drugs, injury, anoxia or high concentrations of carbon dioxide. Hypoventilation may also be caused by conditions more directly affecting the respiratory muscles or even the lungs themselves, e.g., diaphragmatic paralysis, inability to fix the costal cage in small premature infants, and respiratory obstruction from various causes.

Persistent hypoventilation is one of the leading causes of death in the neonatal period. The principal clinical manifestations are related to the inadequate respiratory effort, viz., gasping, shallow, irregular respiratory movements with little exchange of air. Severe cyanosis, bradycardia and poor muscle tone are also present.

The changes in the chemical constituents of the blood include a reduction in oxygen and pH and an elevation of carbon dioxide and lactic acid in the plasma.[2, 3] Since the arterial pCO_2 is elevated, oxygen rather than a mixture of oxygen and carbon dioxide would appear to be the gas of choice in the treatment of such infants.

The syndrome referred to as *pulmonary hyaline membranes* constitutes an important cause of respiratory distress during the early neonatal period. It is most liable to occur in premature infants, in infants delivered by cesarean section and in infants of diabetic or "prediabetic" mothers, although occasionally it is seen following apparently normal deliveries. Respiratory difficulty may be noted immediately after birth or may develop during the first few hours of life. It is manifested by

increased respiratory rate, increased irregularity of the respiratory pattern, grunting respirations, suprasternal and/or infrasternal retractions and cyanosis. Rales and poor aeration of the lungs are inconstant in the early stages, but are characteristically present before death. Tachycardia is followed by brachycardia in the terminal phases. Hypotonia, hyporeflexia, hypothermia and hepatomegaly may be noted. Roentgenographic studies reveal a diffuse, fine, reticular pattern throughout the lung fields with increasing opacification of the lungs in those infants who die.

Karlberg et al.[5] demonstrated that the respiratory distress associated with pulmonary hyaline membranes is accompanied by an increase in the respiratory rate, minute volume and functional pulmonary dead space and by normal tidal volume and alveolar ventilation. Using intraesophageal pressure as an indication of intrapleural pressure, they noted that these infants exerted four to 10 times the amount of energy used in normal respiration. The increased minute volume is further enhanced by the inspiration of high concentrations of oxygen; this occurs as a result of an increase in tidal volume rather than as a result of further increases in the respiratory rate.

The alterations in the chemical constituents of the blood in infants with pulmonary hyaline membranes syndrome may be those of respiratory acidosis, i.e., increase in plasma pCO_2 and decrease in pH. The increase in pCO_2 indicates that alveolar ventilation is not normal. Furthermore, in contrast to the respiratory acidosis encountered in older children and in adults, the $[BHCO_3]$ is disproportionately low as compared to the level of carbon dioxide. This might be expected, since the $[BHCO_3]$ of normal infants immediately after birth is usually in the vicinity of 19 to 20 mEq. per liter, whereas that of adults is usually about 25 mEq. As a result, respiratory acidosis in the newborn infant associated with even small changes in pCO_2 will be accompanied by more striking alterations in the proportion of $[BHCO_3]/[H_2CO_3]$ with a corresponding significant decrease in pH. Thus, although the total carbon dioxide as measured in the blood may be within normal limits, measurement of the pH and calculation of the $[H_2CO_3]$ and $[BHCO_3]$ reveals the significant abnormalities. The acidosis in infants with pulmonary hyaline membranes syndrome becomes progressively more severe, and in the terminal stages the plasma pH may fall to levels of 7.00 or lower.

Infants of diabetic and "prediabetic" mothers with pulmonary hyaline membranes have alterations in the chemical constituents of their blood as noted above.[7] In addition, low levels of blood sugar may be encountered during the first one to two hours after birth and may persist during the first 10 days of life.[12] Infants of diabetic mothers with neither acidosis nor hypoglycemia are usually asymptomatic, whereas

those with both acidosis and hypoglycemia usually exhibit progressive respiratory distress associated with pulmonary hyaline membranes.[9]

Less frequent causes of respiratory distress associated with an increased pCO_2 and hypoxia in the newborn infant include diaphragmatic paralysis, pneumonia, pneumothorax and pulmonary cysts. The chemical changes associated with such intracranial lesions as intraventricular hemorrhage and with various cardiovascular malformations have not been studied in detail in the immediate neonatal period.

In general, *correction* of respiratory disorders in newborn infants with hypoxia and elevation of pCO_2 is directed at improvement of the oxygenation of the blood and at correcting the underlying disease. The administration of oxygen will improve oxygenation of the blood (except in infants with right-to-left cardiac shunts), but the pCO_2 will not return to normal unless the underlying disease is corrected.

Slight elevation of plasma pCO_2 may be of little significance, as exemplified by the occurrence of mild respiratory acidosis in a certain percentage of apparently healthy premature infants. However, severe elevations of pCO_2 may be of greater significance in the immediate neonatal period than in older children and adults, since some of these infants have both a metabolic and respiratory acidosis with no adequate method for compensation of either defect, and are thus unable to prevent a significant lowering of the pH. The resultant acidosis may lead to irreversible damage. In addition, striking elevations of plasma pCO_2 may depress the respiratory center with subsequent depression of respiration.

Decreased pCO_2

The chemical findings associated with *respiratory alkalosis* are present in about 10 per cent of apparently healthy premature infants, and *combined metabolic acidosis* and *respiratory alkalosis* are present in approximately two thirds of healthy full term infants in the first four days of life. Nevertheless, respiratory distress associated with a primary decrease in alveolar and thus in plasma carbon dioxide (respiratory alkalosis) is uncommon in newborn infants. The more common causes of hyperventilation in older children, e.g., encephalitis, cerebral edema, cerebral trauma or damage from a noxious drug, are either not encountered during this period or appear to result in depression rather than stimulation of the respiratory center. Thus the untoward effect of analgesic drugs administered to the mother is that of narcosis with hypoventilation in the infant rather than the reverse. Possibly certain types of cerebral damage occurring before or during delivery might cause hyperventilation and respiratory alkalosis, but to date the occurrence of such a phenomenon has not been recognized.

Hyperventilation associated with *metabolic acidosis* is encountered in newborn infants after the fourth day of life, but only infrequently prior to this time. It is occasionally observed, however, in infants of diabetic or "prediabetic" mothers in the immediate postnatal period, when it is associated with a respiratory rate greater than 50 per minute, and with slight costal retractions without cyanosis. The plasma pH, carbon dioxide content and pCO_2 are decreased, the values sometimes being as low as 7.27, 13 mEq. per liter and 29 mm. of mercury, respectively. The low pCO_2 indicates adequate alveolar ventilation. It is practically impossible to differentiate this condition from the syndrome associated with pulmonary hyaline membranes except by chemical studies. In the latter condition there is elevation of plasma pCO_2 which indicates hypoventilation.

Hyperventilation with metabolic acidosis is also observed in newborn infants with severe diarrhea or with acute adrenal insufficiency secondary to massive hemorrhage or sepsis. Its occurrence in association with other diseases such as diabetes mellitus in the infant, congenital adrenal hyperplasia or adrenal hypoplasia with resultant salt and water deficiency and bilateral renal hypoplasia is well recognized, but clinical and chemical studies are usually not diagnostic until after the fourth day of life.

SUMMARY

The basic concepts of respiratory physiology as reflected in the blood chemical stimuli of respiration (pCO_2, pH and pO_2) have been reviewed, and the alterations in apparently normal newborn premature and full term infants have been discussed.

The usual chemical findings in association with respiratory distress in the immediate neonatal period are those of combined metabolic and respiratory acidosis, with decreased pH and [$BHCO_3$] and elevation of the pCO_2. Increase in plasma pCO_2 occurs in association with a variety of respiratory disorders in the newborn period, including asphyxia neonatorum, cerebral depression and pulmonary hyaline membranes syndrome, and indicates that alveolar ventilation is abnormal, but does not serve to differentiate the basic cause of the respiratory distress. Recognition of its occurrence and correction when possible are important since the acidosis may lead to irreversible damage and high levels of plasma pCO_2 may lead to respiratory depression.

Severe metabolic acidosis is infrequently encountered in newborn infants with respiratory distress prior to the fourth day of life, although it may sometimes be observed in infants of diabetic or "prediabetic" mothers or in infants with severe diarrhea or acute adrenal insufficiency secondary to massive hemorrhage or sepsis.

Many of the basic concepts of respiratory physiology expressed in this clinic are those of C. F. Schmidt: *MacLeod's Physiology in Modern Medicine*. St. Louis, C. V. Mosby Company, 1941.

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CLINICAL EVALUATION OF RESPIRATORY FUNCTION IN NEWBORN INFANTS

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The first few hours and days after birth are among the most critical in any person's life. One to 2 per cent of the population die during the first week, and the morbidity rate for serious conditions is easily double the mortality rate. Most of the difficulties that arise during this period relate to disturbances in respiration, making the clinical evaluation of this function a matter of the greatest importance. Heretofore clinicians looked for cyanosis and dyspnea in appraising respiratory function in the newborn, but their confidence in their observations was never great. The fact that cyanosis and dyspnea disappeared within a few minutes of birth did not relieve the observer's mind, since experience showed that some infants might appear well shortly after birth, only to exhibit signs of respiratory distress later. Clinical experience also indicated that cyanosis and dyspnea could persist for a considerable time after birth and subsequently disappear. Because clinicians could never be sure, they frequently placed all small premature infants in high concentrations of oxygen for varying periods of time regardless of their needs at the moment. This reliance on birth weight as an indication for oxygen therapy was the best they could do, but it was not very rational. Birth weight is not a measure of respiratory function and cannot help in determining which infants of the same birth weight will survive or die. The need for objective, reliable, easily applied methods for differentiating not only infants with severe respiratory insufficiency, but also those with milder degrees of the syndrome, from normal infants was self-evident.

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Studies in this Clinic during the past few years have produced a method for evaluating respiratory function in newborn infants that not only is objective, but also appears to be reliable and easy to apply. The method consists in counting the respiratory rate at frequent intervals after birth under resting conditions and determining the trend of the respiratory rate. The method can be applied to premature and full term infants alike and, when combined with other observations, appears to have a high degree of reliability. The following account describes its use in several hundred infants in this Clinic and discusses some of the physiological and anatomical changes associated with variations in the trend of the respiratory rate.

SIGNIFICANCE OF THE RESPIRATORY RATE

Newborn infants can be divided into three groups, depending on the trend of their respiratory rates. Group I consists of infants who

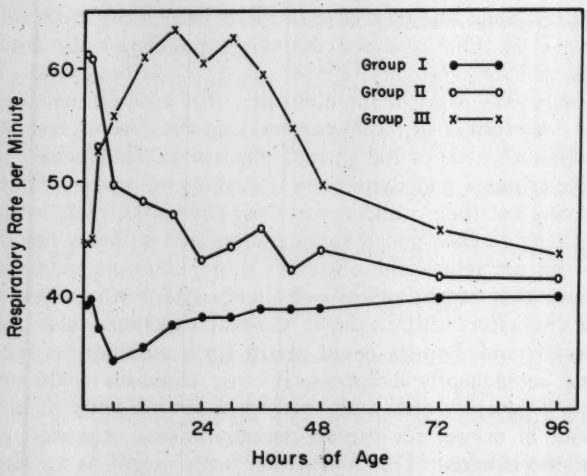

Fig. 3. Variations in the trend of respiratory rates among newborn infants.

breathe at approximately 40 per minute from birth on without significant fluctuations in rate. A significant fluctuation in rate has been arbitrarily defined as one in which the mean rate for a given age period varies by 15 or more respirations per minute as compared to the average rate obtained during the first hour after birth. Group II includes all infants whose rates are high the first hour, usually over 60 per minute, show no significant increase after the first hour and subsequently decrease to normal levels, usually within a few hours or a day or two of their birth. Group III consists of all infants whose respiratory

rates show a significant increase after the first hour. Figure 3 illustrates the trends of the respiratory rates in the three groups and is based on a large series of observations.[1, 2, 3]

All three trends are observed in premature and full term infants, although the incidence of the three trends among the latter differs from that among premature infants. Most full term infants belong to either group I or II, and something less than 5 per cent of full term infants can be classified in group III. The incidence of the three trends among premature infants is shown by the data in Table 3, based on a study of 229 premature infants consecutively born in this hospital, not including those with major anomalies or hemolytic disease of the newborn. The 229 infants were about equally divided among the three respiratory groups. The number of premature infants in groups I and II decreased with the birth weight, while infants in group III were about equally distributed among the three birth-weight groups.

TABLE 3. *Hebdomedal Deaths According to Birth Weight and Respiratory Group*

RESPIRATORY GROUP	BIRTH WEIGHT—GM. 1001–1500 Born	Died	1501–2000 Born	Died	2001–2500 Born	Died	Total Born	Died
I	2	0	8	0	63	0	73	0
II	2	0	20	0	61	0	83	0
III	23	10	26	6	24	2	73	18

MORTALITY

The deaths in the three respiratory groups by birth weights are also shown in Table 3. There were no deaths in groups I and II. All 18 deaths occurred in group III, most of them in the lower birth-weight brackets. Five infants died while their respiratory rates were increasing, and all had extensive pulmonary hyaline membranes; the longest any one of the five lived was 60 hours. Thirteen died while their respiratory rates were returning to normal or after they had reached normal levels; three died when less than 60 hours of age, two with pneumonia and sclerema and one with a brain hemorrhage. Among the ten who died after 60 hours of age three had kernicterus, unrelated to any blood incompatability in two instances and unrelated to any Rh factor in the third; four had pneumonia; two had brain hemorrhages; and one infant had no autopsy. The study covered a period of almost two years, during which time there were approximately 3000 births in this hospital. During this same period there were five deaths among full term infants exclusive of those associated with major anomalies and hemolytic disease of the newborn. These five infants also belonged to group III.

Three died with pneumonia, one had sclerema and a brain hemorrhage, and the other had pneumonia and a brain hemorrhage. All died during the first week. The nature of the underlying anatomical changes could not be predicted from the height to which the respiratory rates rose or the duration of the elevation of the respiratory rates. A significant increase in respiratory rate simply indicated that the infant was in a group in which the mortality rate in the first week was high regardless of his birth weight. If the infant was a premature infant and died while the respiratory rate was increasing, there was an excellent chance that pulmonary hyaline membranes would be found at autopsy.

CYANOSIS

Cyanosis was observed only during the first few minutes after birth among infants in groups I and II. About half the infants in group III

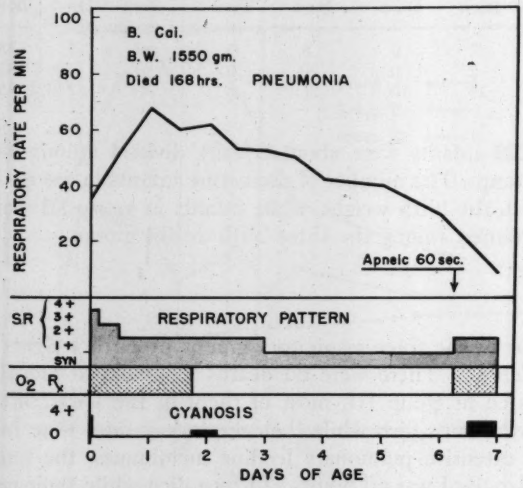

Fig. 4. Clinical course of Baby Cai. Simple retraction—*SR*; synchronous respiratory pattern—*SYN*.

had cyanosis which persisted after birth or recurred later during the first week. Recovery in these infants could not be predicted from the height to which the respiratory rate rose. Infants survived who respired at 140 per minute, and others died even though the rate increased to only 60. Figure 4 illustrates the course of an infant in group III who survived the respiratory distress of the first 24 hours, subsequently improved to the point of being free of cyanosis when out of oxygen, breathed at a normal rate without signs of retraction from the third to sixth day, and became cyanotic and died on the seventh day as a

result of pneumonia. The course of this infant is a good illustration of several important facts: infants in group III are not past the danger point just because they appear to recover from their distress of the first day or two; the height of the rate does not determine survival; deaths that occur after the respiratory rate has started to decline or has returned to normal are almost always accompanied by a further slowing of the respiratory rate to less than 30 per minute and the sudden appearance of severe and prolonged periods of apnea.

About half of the infants in group III showed no evidence of cyanosis at any time. These infants presumably had respiratory insufficiency in a milder form than the others. The fact that their respiratory rates increased significantly after birth kept them under closer surveillance by nursing and medical staffs for at least the first week, because experience in this Clinic has shown that trouble can be expected from any infant in group III during this period. The trouble can be in the form of sudden, serious respiratory insufficiency or the development of hyperbilirubinemia unassociated with any blood group incompatibility.*

Not all cyanosis in newborn infants is serious. The localized cyanosis often seen about the head and not elsewhere is probably the result of a localized disturbance in the capillaries, perhaps caused by undue pressure during pregnancy or delivery. This type of cyanosis does not respond to oxygen therapy, but disappears of its own accord after several days. Newborn infants occasionally exhibit cyanosis only of the hands and feet; this type of change is also dependent on local conditions in the skin and not on a general reduction of oxygen saturation of the blood. Asphyxia pallida is another term for shock and may be caused by a number of things, such as blood loss, severe injury or severe respiratory insufficiency. These infants appear pale, and the skin has a gray cast, the mucous membranes being dark. It is an indication of a serious disturbance and of poor prognosis. It is much less common than the generalized cyanosis of the skin and mucous membranes usually associated with respiratory insufficiency.

APNEA

Sudden, prolonged apnea resulting sometimes in death is not uncommon among newborn infants with respiratory insufficiency. It has not been encountered among infants in groups I and II, but is restricted to infants in group III, especially those with birth weights under 1500 gm.* These prolonged periods of apnea can occur during the first week, usually after the third day; if the infant survives the first week without exhibiting them, they are not likely to occur after the first week. Sometimes a respiratory rate that falls below 30 per minute is a

* H. C. Miller: Unpublished studies.

warning sign of impending disaster. Respiratory rates below 30 per minute and even below 20 per minute are well tolerated by infants in groups I and II and by most infants in group III who weigh more than 1500 gm. at birth, but not by the smaller premature infants in group III. Any small premature infant in group III whose respiratory rate falls below 30 per minute should be watched closely; few such infants survive if their respiratory rates fall below 20 per minute.

Sudden, profound apnea occurs in these small premature infants belonging to group III when least suspected. The infant whose course is illustrated in Figure 4 is a good example.

This infant had recovered from the initial respiratory distress of the first two days and appeared to be doing well, breathing easily without cyanosis and at a normal rate. On the sixth day the respiratory rate began to fall to 30 or less per minute, and a sudden bout of apnea occurred lasting a minute and accompanied by cyanosis. The respiratory rate continued to fall, and the infant died a few hours later.

Slowing down of the respiratory rate with increased periods of apnea is typical of the response of infants who die on the second or third day after birth regardless of whether the infant has pneumonia, kernicterus or a cerebral hemorrhage.

Infants in group III who are going to get into trouble from abnormal slowing of the respiratory rates and the appearance of severe apnea almost invariably do so some time before the end of the first week, and usually they have recovered sufficiently by the end of the first week to be out of danger. That such is not always the case is illustrated by the course of the infant shown in Figure 5.

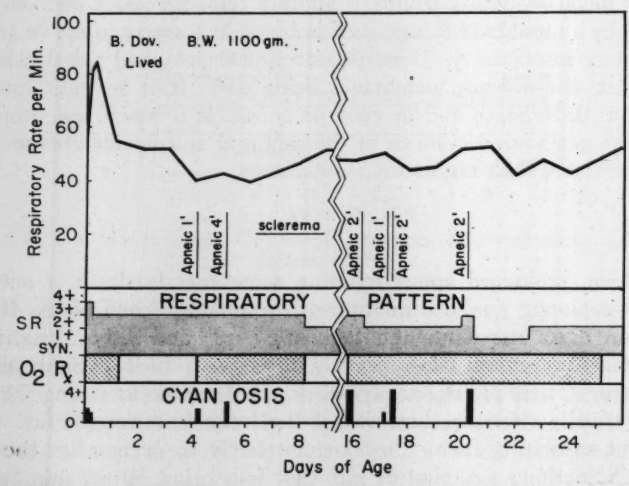

Fig. 5. Clinical course of Baby Dov. Simple retraction—SR; synchronous respiratory pattern—SYN.

This infant continued to have prolonged apneic periods through the first three weeks in spite of the fact he was breathing 40 per cent oxygen. This infant could be stimulated to breathe when in one of his profound periods of apnea by snapping the soles of his feet or by other sensory stimuli.

It is rather amazing to see some of these infants maintain a good color even though they are apneic for 30 or 40 seconds at a time, but cyanosis eventually appears if the period of apnea persists.

The cause of the fast and slow respiratory rates in newborn infants has not been established. It has been presumed that hypoxemia was the cause of the infants' respiratory distress and fast rates, but more critical evaluation of the effects of hypoxia on newborn infants has shown that it depresses respiratory activity and does not stimulate it.[4, 5] It is much easier to believe that hypoxemia accounts for the slow respiratory rates encountered among infants in group III than for the high rates. Infants in group III have a decided tendency towards an uncompensated respiratory acidosis.[6] They also have greater difficulty maintaining a normal acid-base balance than they do oxygenating their blood. They likewise have reduced tidal volumes.[3] The increase in respiratory rates may be dependent on their efforts to adjust acid-base equilibrium in the presence of a restricted tidal volume. More study will be needed before the cause of the abnormal respiratory rates, both fast and slow, has been established.

DYSPNEA

The normal, healthy newborn infant breathes with a synchronous expansion of chest and abdomen and without signs of retraction during the first two or three days after birth. With increasing age *normal* infants begin to show signs of retraction on inspiration, and this persists as a *normal* finding for several weeks and months, presumably the result of an increase in the vigor of contraction of the diaphragm.[7] Infants with respiratory insufficiency exhibit signs of retraction during the first two or three days and then, like normal infants, continue to retract as they get older.

Retraction of the chest wall takes one of two general forms. In one the lower end of the sternum and the lower chest wall along the attachment of the diaphragm are pulled inwards as the upper chest and abdomen expand, so-called simple retraction, and in the other the whole anterior chest wall is pulled down towards the abdomen and inwards as the abdomen expands. The latter has been labelled seesaw breathing. Occasionally a third type is seen; it consists in an exaggerated expansion of the upper chest and practically no expansion of the abdomen; the lower costal margin tends to curl under. This type is not common, but usually appears right after birth, and the survival rate is low among infants exhibiting it.

The presence of retraction during the first two or three days indicates respiratory insufficiency. However, it is not a helpful sign in trying to make a prognosis, because no one has succeeded in measuring the amount of retraction objectively and correlating the results with the outcome. The best that can be done is to estimate the amount of dyspnea on the basis of 1 to 4 plus, or mild, moderate and severe. But the correlation between such measurements with the outcome for the infant has not been too helpful or satisfactory. The absence of any retraction during the first two or three days is a helpful sign in premature infants whose birth weights are less than 2000 gm. If their respiratory rates are normal and they are free of cyanosis and not retracting, the prognosis for survival is good.

RESPIRATORY RHYTHMS

Normal infants breathe with regular rhythms during the first two or three days after birth.[7] On the other hand, irregular rhythms during this same period are common among infants with respiratory insufficiency. All infants, both normal and sick, tend to have irregular rhythms as they get older. By the end of the first week most infants show considerable irregularity in their respiratory rhythms, and they fluctuate between regular and irregular rhythms suddenly and often, frequently without apparent explanation. This behavior continues for several weeks. Its cause is not well understood. Pneumographic tracings indicate that the irregularities may be gross or fall into a fairly regular pattern of periodic breathing with fairly uniform intervals of apnea.

OTHER FINDINGS

The degree of muscle tone in a newborn infant is almost certainly related to the degree of hypoxemia and hence to the degree of respiratory insufficiency. Behrle and Smull* in this Clinic have found that somatic activity is diminished in newborn infants who are hypoxemic, while older infants become quite the opposite and grow more restless. Lack of or impaired muscle tone probably can be attributed to other factors than hypoxemia, but the latter must be given consideration whenever newborn infants appear hypotonic. No correlations have yet been attempted between the degree of hypotonia and the amount of hypoxemia.

An expiratory grunt is not uncommon among infants with severe respiratory insufficiency and, when present, indicates a poor prognosis.

Auscultation and percussion of the chest have not been stressed in the studies conducted in this Clinic during the last few years. Certainly the presence of rales throughout the chest is more common among in-

* F. C. Behrle and N. W. Smull: Unpublished data.

fants in group III than in those in groups I and II. In the latter two groups rales are sometimes present right after birth, but they disappear within a few minutes. The volume of air exchanged in infants in groups I and II is larger per unit of body weight than among infants in group III; consequently breath sounds tend to be more pronounced and percussion to be more resonant in the former. These findings, like cyanosis and dyspnea, are difficult to quantitate, and their interpretation necessarily contains a large subjective element, making it difficult to correlate them with other measurable factors.

METHODS OF MEASUREMENT AND RECORDING

The technique for measuring the respiratory rate is simple. It consists in placing the infant without clothes in an Isolette or other incubator allowing good visibility, and counting the respiratory rate for a full minute. If the baby is restless and not quiet or asleep, the results are not acceptable except during the first hour after birth, when restlessness is almost universal. To establish the trend of the respiratory rate, the practice in this Clinic has been to count the respiratory rate every 15 minutes the first hour, every two hours the next 47 hours and every four hours for the next 48 hours. The nurse or attendant also makes a note each time the rate is counted of the infant's color, respiratory rhythm, respiratory pattern, muscle tone and somatic activity. If the infant is receiving oxygen, the concentration in the incubator is measured each time the rate is counted. A regular chart is kept on each infant until the trend of the respiratory rate has been definitely established or until all danger is considered to be past. Keeping such a record entails little additional work for the attendants and ensures a minimum of observation on a group facing a high risk. Such records are kept routinely on all premature infants in this Clinic and any full term infants for whom there may be any concern.

TREATMENT

Infants whose cyanosis does not clear up with the first few breaths and in the first few minutes after birth are placed in an atmosphere of 40 per cent oxygen until they demonstrate their ability to maintain a good color while breathing room air. A respiratory record is started on all such infants. Oxygen therapy has not been required beyond the first few minutes after birth for infants belonging to groups I and II. If the infant breathes at about 40 per minute, is free of cyanosis within 10 minutes or less of its birth and is not retracting, the chances are excellent that it will turn out to be in group I. On the other hand, if cyanosis persists beyond the first 10 minutes, the chances are excellent

that the respiratory rate will show a significant increase in the next few hours, putting the infant in group III. If the infant is not cyanotic and if the respiratory rate shows a significant increase, the infant qualifies for group III and is considered a sick infant until at least the end of the first week. If cyanosis develops in such an infant, 40 per cent oxygen is administered continuously. Oxygen therapy is discontinued on infants in group III when they demonstrate they can remain acyanotic while breathing room air and if their average respiratory rate is over 30 per minute.

CONCLUSIONS

The respiratory rate is an easy measurement to make on newborn infants who are quiet or asleep and are undressed in an Isolette or other incubator providing good visibility.

The trend of the respiratory rate during the first few hours and days after birth is a highly reliable and objective method of evaluating respiratory function.

Infants whose respiratory rates show a significant increase during the first few hours after birth have a mortality rate of 25 per cent during the first week. Respiratory deaths and cyanosis have not been encountered in newborn infants unless their respiratory rates show a significant upward trend after birth.

The trend of the respiratory rate in conjunction with the presence or absence of cyanosis and dyspnea is useful in planning oxygen therapy for newborn infants.

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ROENTGEN DIAGNOSIS OF PULMONARY DISEASE OF THE NEWBORN INFANT

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One of the first considerations to arise, when a newborn infant exhibits respiratory symptoms, is an x-ray examination. Frequently, significant information is obtained for the diagnosis and management of the cause for the infant's symptoms; at other times the examination provides no useful information or, through misinterpretation, leads to unnecessary procedures or to failure to utilize potentially beneficial procedures. For various reasons the clinician, be he obstetrician, pediatrician or general practitioner, is often required personally to evaluate the films from such examinations. An appreciation of the limitations as well as the values of the radiographic investigation in the diagnosis of pulmonary pathology in newborns is necessary for all concerned. These limitations are in great part due to the special nature and course of the diseases, which are often so different from those observed in later life, and to the wide range of variations in the roentgen appearance of normal intrathoracic structures in neonates. It is in view of these peculiarities that the roentgenological picture constantly has to be correlated with the clinical history and findings and evaluated in the light of knowledge of diseases and organ response that are peculiar to the newborn. Congenital anomalies are, for obvious reasons, much more prominent and significant here than in older persons. Moreover, conditions which are not strictly "pulmonary diseases," but are associated with respiratory symptoms, must also come under consideration.

In the following paragraphs some of the normal variations and the

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roentgen changes of the most important diseases will be discussed. Only brief mention will be made of some of the rarer entities. The data have been drawn from our own material and from the available literature. When films of newborns were not readily available, comparable roentgenograms of slightly older infants have been used for illustrations; these substitutions are indicated in the legends.

TECHNICAL CONSIDERATIONS

Proper technique is of the utmost importance. In ideal circumstances short exposure times and relatively high milliamperage are used (e.g., $\frac{1}{60}$ second and 400 to 500 milliamperes). Films are exposed during the inspiratory phase of respiration with the patient preferably upright and at 6 feet from the tube. Satisfactory results can, however, be obtained, in many instances, with less specialized apparatus, shorter distances and with the patient recumbent. The newborn can be brought to the x-ray department and radiographed in specially designed cribs. Special bedside units, still capable of relatively short exposure times, can also be used. Separate standards for cardiac size, levels of diaphragms, and so on, must be used for films taken upright or recumbent, with 72-inch or 36-inch or less tube distances, and with posteroanterior or anteroposterior penetration of the x-rays. A relatively large central mediastinal shadow is favored by recumbency, short tube distances and anteroposterior penetration of x-rays; elevation of the diaphragm is exaggerated in recumbency. However, if these differences are kept in mind, one can develop satisfactory proficiency in the interpretation of infants' films so long as the technique is consistent or known. Control of phase of respiration during exposure is extremely difficult, but can be improved by separate rotor switches to permit instantaneous exposure.

Additional views to the routine frontal and lateral projections, and fluoroscopy, with swallow or introduction into the esophagus of opaque material, are often indicated. The dynamics of the thorax and intrathoracic structures during quiet breathing and crying can be evaluated only fluoroscopically. Fluoroscopy, in addition, is often crucial in determining position, contours and behavior of unusual intrathoracic shadows. The exposures, however, should always be kept to a minimum consistent with adequate diagnosis, because it is almost impossible to examine the infant without radiating the entire body.

THE NORMAL CHEST

Thoracic Cage

Before the onset of respiration and in stillborns (Fig. 6) the thorax has a conical or bell-shaped configuration; the ribs have a downward

inclination and form an acute angle with the spine. With the onset of respiration, and expansion of the lungs, the thorax rapidly assumes the normal infantile configuration. The ribs come to lie horizontally, and the thorax becomes rounded with practically equal anteroposterior and transverse diameters. A marked bell-shaped thorax is considered abnormal. This deformity is often seen in the presence of neuromuscular abnormalities from any cause, or a severe pulmonary disease characterized mainly by decreased lung volume. In a mild degree, however, this thoracic configuration can sometimes be observed in apparently normal newborns.

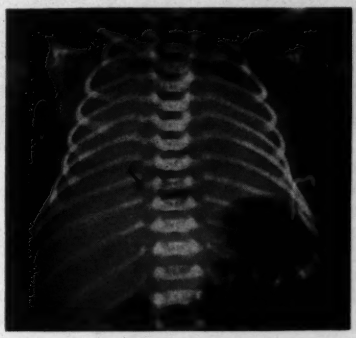

Fig. 6. *Bell-shaped thorax.* Primary atelectasis (failure of lung expansion) in a premature male infant. The heart is invisible because there is no air in the lungs to outline its margins.

Lungs

The question whether normal lungs aerate fully at birth, or over a period of several days or even weeks, has not yet been settled conclusively. References to papers on this subject can be found in works by Smith[63] and Peterson et al.[50] In view of the recent increase in knowledge and the recognition of more types of diseases which cause respiratory distress in the neonatal period, and of their milder forms, it is becoming clearer that, in the majority of normal newborns, inflation of the lungs probably is complete after the first few breaths. In some apparently normal babies, however, the diaphragm may remain slightly elevated and the lungs may continue to show, for a few days after birth, a slight decrease in their volume. Radiographs of such infants show crowding of the lung markings, as if the chest were in constant expiration. These are usually babies with shallow respiratory excursions. Whether maternal oversedation, subclinical hypoxia or prolonged and difficult delivery has anything to do in the causation of these changes is not known. These exaggerated lung markings may even be vascular in origin and be related to patency of the ductus arteriosus or to the vascular adjustments that take place in the lungs of newborns.

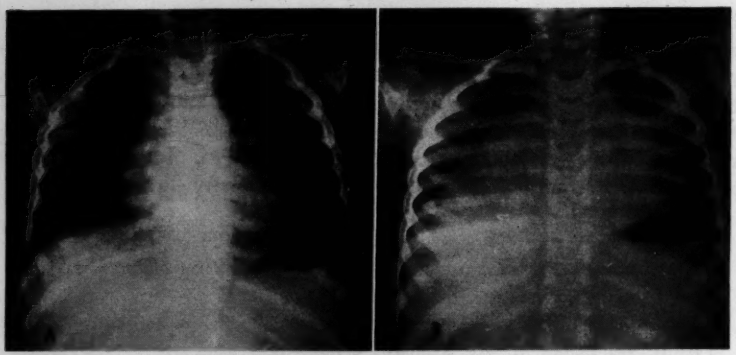

Fig. 7. *Effect of exposure* during different phases of respiration on pulmonary aeration, position of diaphragm and width of the mediastinum. Female, age 5 months. *A*, Inspiration; *B*, expiration.

Striking roentgen changes in the lungs occur during respiration (Fig. 7). In deep expiration one notes elevation of the diaphragm, diminution of the pulmonary volume and air content and an apparent accentuation of the intrapulmonary shadows. Similar changes are also seen in the presence of a high diaphragm from any other cause. The opposite occurs in full inspiration.

Thymus

The thymus may vary considerably in size and shape in normal infants; sometimes even in newborns its shadow is large and causes widening of the mediastinum on one side or bilaterally (Fig. 8). Occasionally the thymus extends downward into the cardiophrenic angles and completely obscures the cardiac silhouette. The mediastinal widening may be smooth or globular; in some instances one or both thymic lobes project outward into the lungs like a sail. The shadow of the thymus is exaggerated in expiration (Fig. 7). The thymus can be best identified fluoroscopically. The notches or steps commonly formed by its lobes on the cardiac contours are quite characteristic. These notches move upward along the borders of the heart in inspiration at the same time that the heart is pulled downward by the diaphragm, and vice versa. Occasionally the thymus cannot be separated from the heart or other mediastinal shadows. Diagnostic pneumomediastinum has been advocated[15] in questionable cases, but this procedure is seldom used.

Great Vessels

Identification of the main pulmonary artery, in the films or at fluoroscopy, is often impossible because of the overlying thymic shadow.

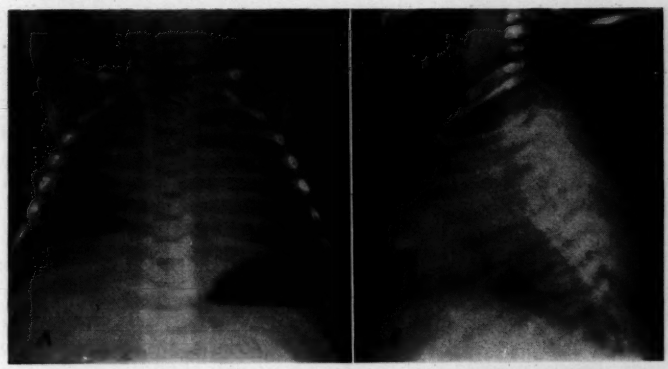

Fig. 8. *Thymus, trachea and retropharyngeal space* in a 7 week old male infant. *A*, Frontal projection. Note normal deviation of the trachea toward the right (upper arrows) and the notches produced by the thymus on the cardiac borders (lower arrows). *B*, Lateral projection. The anterior mediastinal position and the sharp lower border are characteristic of the thymus. Note normal tracheal buckling (lower arrow), exaggerated in expiration, and the normal thickness of the retropharyngeal space, at the level of the valleculae (upper arrow).

The position of the aorta generally can be evaluated from the slight indentation this vessel produces on the barium-filled esophagus or from the slight displacement of the trachea toward the opposite side, at the level of the aortic arch.

Trachea and Retropharyngeal Space

The caliber of the trachea varies with respiration. The range of these variations has not been established. It has been stated[16] that, in newborn infants, 3 mm. is the usual minimal tracheal diameter. This measurement is taken in the upper thorax in lateral chest films exposed in inspiration and at 36 inches. The trachea, in addition, normally buckles forward and to the right in expiration, sometimes to a considerable degree (Fig. 8). The width of the retropharyngeal space also varies greatly with respiration, up to one and a half times the anteroposterior diameter of the ossified portion of the fifth cervical vertebral body, at the level of the valleculae.[26]

Heart

Like the thymus, the heart usually seems much larger in expiration than in inspiration (Fig. 7). In most newborns the heart is large even in good inspiration films. In the absence of heart disease or respiratory distress, its size becomes normal in approximately three days.[36, 43] The cause of these changes in size is not clear. Physiological adjustment of

the cardiovascular and respiratory systems to extrauterine conditions may be the main factor.

PULMONARY DISEASES

Hyaline Membrane Disease

This disease has a fairly characteristic roentgen pattern.[50] The changes are apparently constant in all the fatal cases and in most babies who show the clinical findings of hyaline membrane, but who survive. This roentgen picture, when definite, is not seen in the normal, although it has been interpreted[5] as representing primary atelectasis or physiological incomplete expansion of the lungs of the newborn. The thorax is usually normal in size and shape, and the position of the

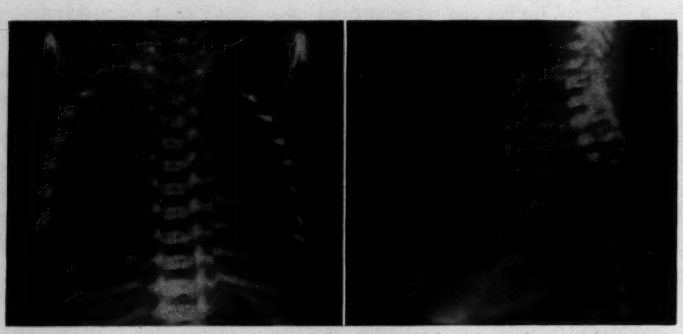

Fig. 9. *Hyaline membrane disease* in a 1 day old male premature infant born of diabetic mother by cesarean section. Autopsy. Note "expanded" thoracic contour despite poorly aerated lung (compare with Fig. 6). A, Frontal projection. Note air bronchogram. B, Lateral projection. The granular or ground-glass appearance of the lung is often more prominent in this projection.

diaphragm is not significantly altered. The lungs have a more or less pronounced granular or ground-glass appearance throughout, which is often better seen in the lateral view, posteriorly (Figs. 9, 10). There may be disproportionate involvement of the two lungs. The over-all air content of the lungs is slightly to definitely decreased, but their volume is not appreciably reduced, except in extreme cases or terminally, when the lungs are small and opaque, and the thorax is bell-shaped (see Fig. 6). Even in these extreme instances, however, the bronchi retain their usual amount of air. Slight cardiac enlargement is generally present. The severity and course of the roentgen picture correspond fairly well to the severity and course of the clinical symptoms and findings. In those patients who survive, clearing takes place gradually over a period of a few days to a week. Complications, such as pneumothorax and mediastinal emphysema, are rare. Changes due to

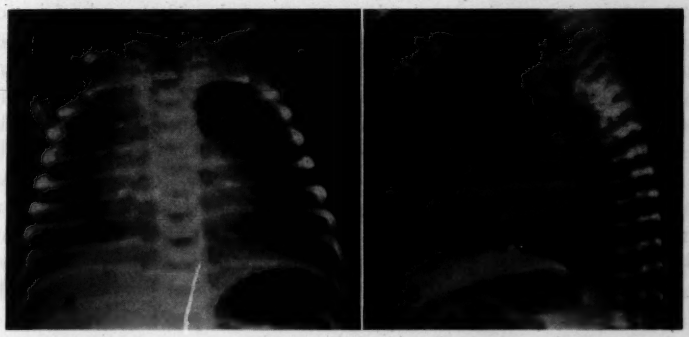

Fig. 10. *Hyaline membrane disease* in 3 day old female infant, full term, cesarean section. Infant survived, so histologic proof is lacking. However, clinical course was typical. Fine granular appearance of lungs is characteristic; compare with Figure 9. A, Frontal projection. B, Lateral projection.

concomitant aspiration of meconium-stained amniotic fluid or superimposed pulmonary inflammatory disease can be suspected roentgenographically when the added features of these complications are present.

Aspiration Syndrome of Postmatures

Postmatures[9] are subject to fetal respiratory distress, and massive intrauterine aspiration of meconium-filled amniotic fluid is considered to be the cause of the lung changes observed in the first days of life. Unlike those produced by hyaline membrane disease, the roentgen findings[50] closely resemble those seen in aspiration of any other material or secondary to certain types of interstitial infection (Fig. 11).

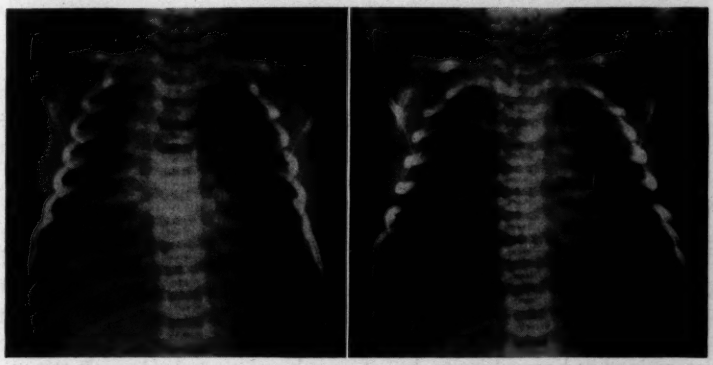

Fig. 11. *Aspiration of the postmaturity syndrome.* A, Frontal projection at age one day. Note pneumothorax on the left. B, Frontal projection at age 3 days. Coarse streaky pattern contrasts with more regular distribution of the densities seen in hyaline membrane disease. Patient improved.

The thoracic cage is commonly overexpanded, and there is elevation of the sternum and flattening of the diaphragm. The lungs show coarse and irregular streaks of increased density fanning out from the hili toward the periphery of the lungs. The severity of the changes varies from case to case. In the more severely affected infants there is also generalized emphysema, irregularity of aeration, and areas of lobular or segmental collapse. Pneumothorax and pneumomediastinum are not uncommon complications. These complications, as well as the basic lung changes, have the tendency to improve rapidly in the patients who survive, in contrast to the slower course of similar roentgen abnormalities secondary to other causes. Superimposed inflammatory disease is not rare. Such complication should be suspected if the duration of the disease is prolonged.

Pneumonia

The lungs of newborns are subject to practically all types of infections seen in older patients. These infections can be acquired in utero,

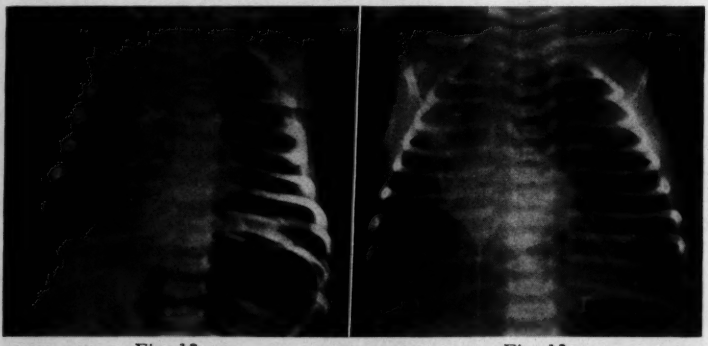

Fig. 12. Fig. 13

Fig. 12. *Aspiration pneumonia* secondary to tracheo-esophageal fistula of "H" type in 3 day old male infant.

Fig. 13. *Aspiration pneumonia* in debilitated female infant at age 6 days. Diffuse pulmonary involvement, collapse of the right upper lobe and shift of the mediastinum towards the right. Right upper lobe involvement is common in recumbent infants.

during labor or postnatally. Frank lobar pneumonia is uncommon in small infants. In infants the lungs usually show more widespread involvement than in older patients. The radiological findings vary considerably. The causal agent of the pulmonary infiltration cannot be determined radiographically, but it may be suggested when all the clinical and laboratory data are correlated. The radiographic method of investigation is more valuable in determining the gross morphology of

the lung changes, their distribution and their complications. There is no constant relation between the degree of severity of the roentgen findings and the amount of respiratory distress observed clinically.

ASPIRATION PNEUMONIA. In massive aspiration of normal and uninfected amniotic fluid the roentgenograms usually show a more or less diffuse clouding of the lungs and, at times, transient collapse of one or more lobes.

Aspiration of oral or gastric secretions, formula or other material commonly leads to lung infection. The roentgen findings (Figs. 12, 13), which are far from specific, vary from exaggeration of the markings, diffuse interstitial thickening and emphysema, to more or less pro-

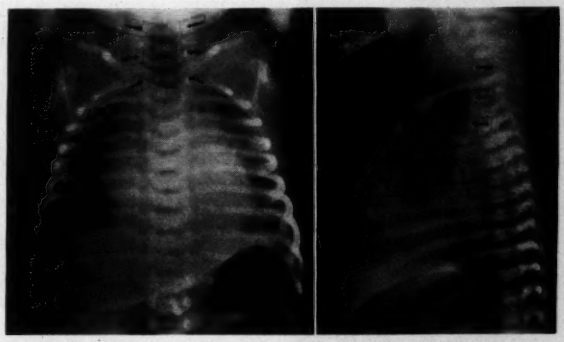

Fig. 14. *Congenital atresia of the esophagus,* with tracheo-esophageal fistula in 6 hour old male infant. *A,* Frontal projection. The arrows point to the dilated esophageal pouch. The air in the bowel indicates that a fistula is present. Mild lung changes of aspiration. *B,* Lateral projection. Note compression and forward displacement of the trachea by the dilated, air-filled, upper esophageal segment. The presenting symptoms in this patient were severe respiratory distress and stridor.

nounced parenchymal patches of infiltration, segmental or lobar infiltration and collapse. In recumbent infants the right upper lobe is more prone to be involved than any other. Local emphysema, pneumothorax and pneumomediastinum may complicate the picture.

Esophageal atresia,[24] with or without tracheo-esophageal fistula, is one of the most important causes of aspiration. In addition to the frequent lung changes of aspiration pneumonia and collapse, films of the chest may show dilatation of the proximal esophageal pouch displacing or compressing the trachea from behind (Fig. 14). Respiratory distress due to tracheal compression by the dilated blind pouch may be the presenting symptom. In the presence of a tracheo-esophageal communication there may be an increased amount of air in the gastrointestinal tract. The diagnosis can be confirmed by the passage of a catheter into the esophagus with or without introduction of contrast substance.

In infants who do not have esophageal atresia, but in whom there is clinical and radiographic evidence of repeated aspiration (Fig. 12), lingering or recurrent pneumonitis or collapse, the radiologist is often asked to rule out tracheo-esophageal fistula of the H type.[18] Abdominal films often show gaseous distention of the bowel (Fig. 15). If a fistulous communication cannot be seen at fluoroscopy after a swallow or introduction into the esophagus of Lipiodol or soluble iodized material, the use of thin barium may be rewarding. The danger of spillage of

Fig. 15. *Tracheo-esophageal fistula* of "H" type (male, 3 days). Same patient as in Figure 12. The gaseous distention of abdomen is common.

small amounts of barium into the tracheobronchial tree has probably been overemphasized.[32] Even if a communication between the esophagus and trachea is not readily established fluoroscopically, several spot films should still be taken with the patient in the lateral semiprone or prone position. Such films may confirm the diagnosis by showing either a thin fistulous tract or a small upward and forward beaklike projection of barium from the esophagus. In rare instances, when these and even more specialized maneuvers fail, surgery may still have to be undertaken, purely on clinical grounds.

One of the most common causes of aspiration is vomiting, especially in debilitated infants. In such infants and in patients with severe nervous system disorders there may be a poor coordination of the swallowing function and spillage of ingested material into the trachea. These

abnormalities may be recognized fluoroscopically when barium is given by mouth to these patients. It is worthy of note in this respect that Lipiodol, like other substances of low surface tension, is often aspirated into the trachea by many normal infants.[18] This possibility should be kept in mind when Lipiodol is used.

Among the unusual causes of aspiration pneumonia which could be diagnosed radiographically, mention is also made of an anomalous lobe of lung arising from the esophagus[21] and a congenital communication between the biliary system and bronchial tree.[47]

STAPHYLOCOCCAL PNEUMONIA. This type of pneumonia in infants gives rise to certain roentgen findings which are often suggestive of the

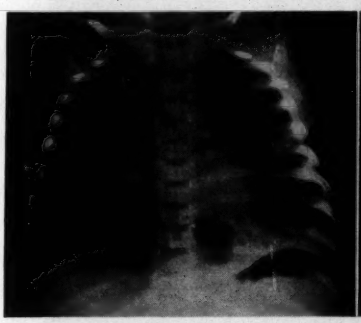

Fig. 16.

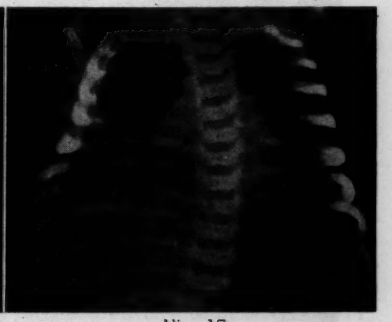

Fig. 17.

Fig. 16. *Staphylococcal pneumonia* in a 2 month old female infant. Soft ill-defined infiltrate in the left lower lobe with adjacent pleural effusion (empyema). Two post-infectious "cysts" are present at the left base.

Fig. 17. *Staphylococcal pneumonia* in a 3 week old female infant. Large postinfectious "cysts" in the right lung

disease.[6, 34, 60] The onset and progression of the changes may be rapid. Radiographically, the pulmonary infiltration may have a streaky interstitial distribution or may be mottled or confluent. Patches of collapse due to bronchial obstruction are common. The salient feature, however, is a pronounced disturbance in aeration. The lungs are irregularly over-expanded and often show areas of obstructive emphysema and "cysts" (Figs. 16, 17). When under tension, these alveolar ectasias, blebs or pneumatoceles may become large and can even displace the mediastinal shadow toward the opposite side. The postinfectious "cysts" are sometimes filled with fluid and often contain air-fluid levels, and occasionally they present thick walls (infiltrated or compressed parenchyma) not unlike pulmonary abscesses. Pulmonary abscesses of various sizes with or without air-fluid levels also occur, but are less frequent complications. The differentiation[6, 53] among lung ectasias, lung abscesses, congenital lung cysts, obstructive emphysema and tension pneumothorax may at

times be difficult. Mediastinal and subcutaneous emphysema, pneumothorax, pyopneumothorax (diffuse or loculated) and bronchopleural fistulas are frequently encountered. Empyema is also a common complication, which may be present from the very beginning of the disease. After surgical drainage of the empyema considerable thickening of the pleural spaces and a nonspecific periosteal new bone formation of adjacent ribs may persist for a long time. Osteomyelitis of the ribs as a complication of surgical drainage has become unusual since the advent of antibiotics. The postinfectious "cysts" may regress in a short time or persist for months without symptoms.

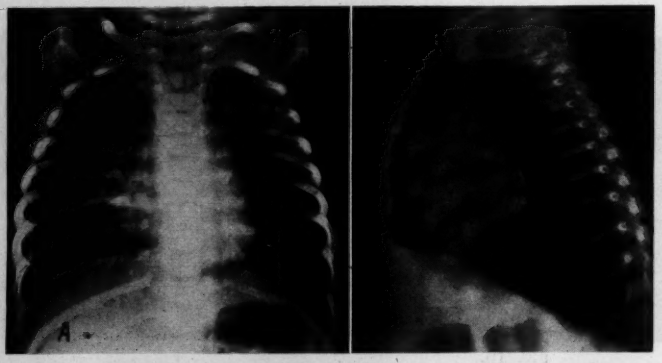

Fig. 18. *Bronchiolitis* in a 2 month old female infant. *A*, Chest, frontal projection. There is generalized emphysema and mild, diffuse interstitial inflammatory reaction. Note small pneumothorax on the left (arrows). *B*, Lateral projection. Note flattening and depression of the diaphragm and increased sagittal diameter of the thorax.

Acute Bronchiolitis (Capillary Bronchitis). The roentgen changes[49, 54] of this disease consist chiefly of an overexpanded thorax, low diaphragm, small heart and generalized, irregular emphysema, often associated with a diffuse exaggeration or thickening of the lung markings or frank interstitial or patchy bronchopneumonia. A miliary type of infiltration has also been described,[49] but is apparently uncommon. At fluoroscopy the lungs are emphysematous and characteristically deaerate poorly in contrast with the overexpanded lungs seen in metabolic hyperventilation. In both bronchiolitis and hyperventilation from any cause, pneumothorax may occur (Fig. 18).

Fibrocystic Disease of the Pancreas (Mucoviscidosis). The earliest findings that can be observed consist of irregular emphysema[35] with poor gaseous exchange and slight exaggeration of the lung markings. This picture gradually worsens with each bout of peribronchial and interstitial infection until the lungs develop the typical and well known roentgen appearance observed in the advanced stage of the disease.[46]

The respiratory symptoms not infrequently start in early infancy, but definite lung changes in the newborn period, detectable radiographically, are seldom seen or suspected.

UNUSUAL TYPES OF PNEUMONIA IN NEWBORNS AND INFANTS. The *interstitial pneumonitis of newborns* described by Adams[1, 2] occurs both in epidemics and sporadically. The disease may be congenital. Prematures are said to be very susceptible. The roentgen changes, as described and illustrated by Adams, resemble those seen in bronchopneumonia from many other causes: increased lung markings; interstitial infiltration, prominent mesially, and patches of bronchopneumonic infiltrates, commonly in the upper lobes. Emphysema, lung ectasias and pleural complications are apparently rare.

Similar findings have been observed in *giant cell pneumonia*,[67, 72] in the type of *pneumonia described by Goodpasture*[23] or in *generalized cytomegalic inclusion disease*,[42] but the cases so far reported are too few to draw a typical roentgen pattern. In one instance[20] of cytomegalic inclusion disease a large pneumonic infiltrate was followed rather rapidly in the same area by large "cysts," for which a lobectomy had to be performed.

Interstitial plasma cell pneumonia affects prematures, debilitated, and hospitalized infants and is said to be due to a protozoon.[65] It commonly occurs in epidemics and has been reported mainly from Europe. The disease is more common during the second and third months of life, but may occur in the newborn period as well. The roentgen findings[22, 33, 59] vary considerably, but seem to consist mainly of an edematous early stage (fine granular appearance of the lungs), diffuse prominence of the lung markings, symmetrical hilifugal densities of infiltration with scattered areas of lobular atelectasis and emphysema. Compensatory emphysema of the lung bases is common. Lung ectasias, pneumothorax and mediastinal emphysema may be encountered. The heart is usually small, and the mediastinum is narrow. Regression of the roentgen changes is slow in the patients who survive.

Fungus pneumonia,[38] *hemorrhagic pneumonia* and *pulmonary hemorrhage*[3, 52] may also occur in newborns and small infants, but so far as we know there is nothing characteristic about their roentgen picture.

PLEURAL DISEASES

Pneumothorax and Pneumomediastinum

Pneumothorax and mediastinal emphysema, together or unassociated, are not uncommon complications of pulmonary or pleural disease. After alveolar rupture due to increased intra-alveolar pressure from any cause, air dissects along the perivascular sheaths[40] and enters the lung roots and mediastinum and may rupture into the pleural cavities. Occasion-

ally air enters the extraparietal intrathoracic pleural spaces or dissects along the fascial planes into the soft tissues of the neck, chest wall and retroperitoneal space. Direct communication between the bronchoalveolar bed and pleuras may also occur through a defect in the visceral pleura after trauma or rupture of a cortical pulmonary abscess or cyst (bronchopleural fistula). A congenital type of bronchopleural fistula has been reported.[28]

Varying degrees of pneumothorax and pneumomediastinum can also be seen in newborns who show no clinical or radiographic evidence of underlying lung disease.[14, 17, 31] This disorder is probably more common than one would infer from the case reports in the literature. The causes of this so-called spontaneous pneumothorax or pneumomediastinum are not clear. Positive pressure resuscitative measures are often incriminated.

Irrespective of the presence or absence of underlying disease, the roentgen changes are the same. In pneumomediastinum one sees a longitudinal radiolucent band along the borders of the mediastinum in the frontal view and a localized collection of air in the anterior mediastinum in the lateral projection.

Pneumothorax is characterized by a radiolucent band of varying width around the lung. If fluid is also present, an air-fluid level is usually seen in the upright position. When the amount of air is large and under tension, the involved hemithorax is entirely radiolucent, the underlying lung is compresed, and the mediastinum is displaced towards the opposite side. Tension pneumothorax is at times indistinguishable from intrapulmonary tension cysts.

Pleural Effusion

Empyema and bronchopleural fistula are common complications of staphylococcal pneumonia and have been discussed earlier. Nonpuru-

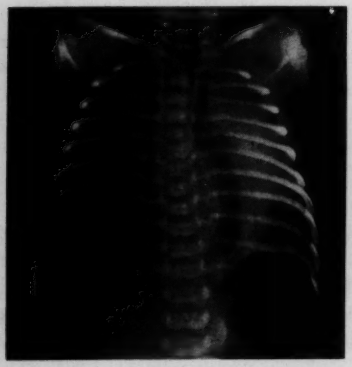

Fig. 19. *Massive pleural effusion* of undetermined etiology in a 6 hour old female infant. The esophagus is filled with air and is displaced towards the left together with the trachea and heart. The left lung is compressed.

lent pleural effusions in the newborn are rare, and the majority of these are probably due to anasarca (from erythroblastosis or other causes) and "spontaneous" chylothorax.[4, 64] At times the origin of such nonpurulent effusions is unknown.[12, 51] We recently observed a newborn infant with massive accumulation of straw-colored fluid in the right hemithorax for which no satisfactory explanation was found at autopsy (Fig. 19).

CONGENITAL ANOMALIES

Lobar Obstructive Emphysema (Localized Hypertrophic Emphysema, Congenital Emphysema)

Respiratory distress in the newborn period may be caused by localized and fixed overdistention of an entire lung, lobe or segment on a

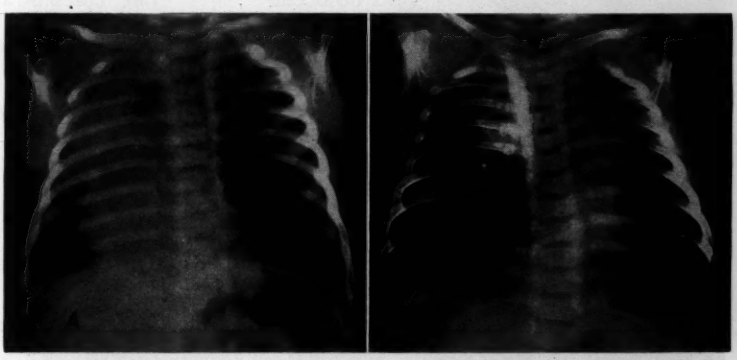

Fig. 20. *Congenital obstructive emphysema.* A, Three week old male infant. The left upper lobe is involved. Note herniation of the affected lung across the midline and displacement of the mediastinum toward the right. Lobectomy. No cause for the obstruction was found in the specimen. B, Two and one-half month old female infant. Obstructive emphysema of the right middle lobe. Lobectomy. No cause for the obstruction found in the specimen.

congenital basis.[37, 62, 69] In severe cases the affected lung may be so markedly overexpanded (Fig. 20) as to displace the mediastinum towards the opposite side and to herniate across the midline anteriorly, especially if a defect in the anterior mediastinum is also present. Distortion and compression of trachea and major bronchi secondary to the overdistended lung may exaggerate the obstruction. At fluoroscopy the involved lung fails to deaerate. The local emphysema is considered ing the affected area. The obstruction may be secondary to bronchial to be due to a check-valve type of obstruction in the bronchus supplystenosis, chondromalacia, a web, localized redundancy of the bronchial mucosa or endobronchial proliferation of aberrant tissue. Narrowing

of the bronchial lumen may also be caused by an enlarged bronchial vessel, by a misplaced left branch of the pulmonary artery,[44, 55, 71] by a large ductus arteriosus or even by a large heart.[30] Extrinsic bronchial compression and localized cartilage deficiency in the bronchial wall may coexist. Not infrequently no cause of obstruction is found in the specimen.

Bronchography is not without risk in severely ill babies. Nevertheless the contrast material may disclose the site of obstruction. In the presence of chondromalacia several films taken during a respiratory cycle may show undue collapse of the involved bronchus.

Congenital Cystic Malformations of the Lungs

It is now fairly well established that the great majority of lung cysts are acquired. Congenital lung cysts do occur,[10, 51, 53, 56] but represent a relatively rare developmental anomaly, probably secondary to faulty canalization of bronchial buds. There are various types of congenital lung cysts. In *multicystic lung disease* (Fig. 21) there are innumerable small cysts involving one lung, lobe or part of a lobe; bilateral involvement is rare. The radiological findings are similar to, if not identical with, those of the so-called *congenital cystic adenomatoid malformation of the lung*[11] (Fig. 22). Communication with the bronchial tree is frequent, and the involved lung shows a mottled or honeycombed appearance. An agglomeration of unaerated cysts may even suggest an intrapulmonary mass. *Solitary cysts* are usually much larger and may also be filled with secretion or air, or both. In the presence of a communication with the bronchial tree, a check-valve type of obstruction often takes place, and, when under tension, the solitary cyst or portion of the affected lung in cystic lung disease may become extremely dilated, compress adjacent lung parenchyma, displace and distort the mediastinal shadows and even herniate across the mediastinum towards the

Fig. 21. *Multicystic lung disease* involving the entire left lung in a 2 day old male infant. Autopsy. Obstructive emphysema is also present. The left lung herniates across the midline anteriorly.

opposite side. A sequestration of the lung,[73] when communicating with a bronchus, may also present as a cystic lesion (Fig. 23).

The differential diagnosis between congenital and acquired cystic lung disease secondary to infection or among congenital solitary cysts, obstructive emphysema under tension, and tension pneumothorax may be difficult.[7, 53] The complications secondary to tension phenomena from various causes are identical. A clear lung on the opposite side and

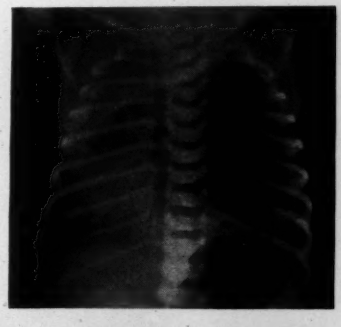

Fig. 22. *Congenital adenomatoid malformation* of the left lung with severe obstructive emphysema. Autopsy. 1 day old male infant.

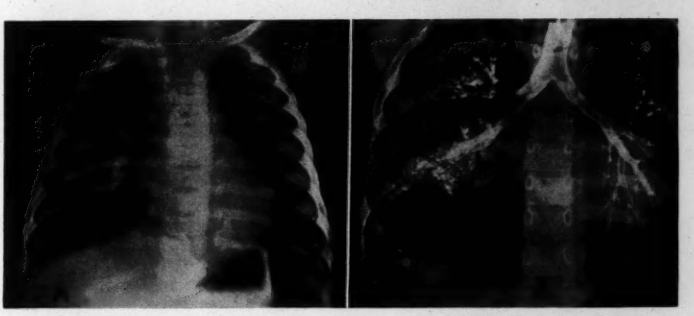

Fig. 23. *Sequestration of the lung.* Female infant. *A,* Chest film at age 7½ months. Cystic rarefaction at the right base (arrows). At fluoroscopy this emphysematous area failed to deaerate. *B,* Bronchogram at age 7 years. Lobectomy. Arterial blood supply from the abdominal aorta found at operation.

many small radiolucent cavities in or around an ill-defined intrapulmonary mass or a large cyst should raise the question of multicystic lung disease or adenomatoid malformation of the lung. Communicating cysts may be filled with contrast material, but bronchography should be undertaken with great caution.

Congenital Diaphragmatic Hernias

Bowel and other intra-abdominal organs can herniate into the thorax through various congenital defects in the diaphragm.[24] The most com-

mon hernias are those that occur posteriorly through the foramina of Bochdalek or through a defect in the posterolateral portion of the diaphragm. Most of these hernias are on the left and have no sac. Less common hernias are those that take place through the parasternal space (space of Larrey or foramina of Morgagni) and the peritoneal-pericardiac hernias;[70] a sac is usually present in these cases. Respiratory symptoms result from compression of lung parenchyma, trachea or major bronchi. Asymptomatic cases are not exceptional. A few or many loops

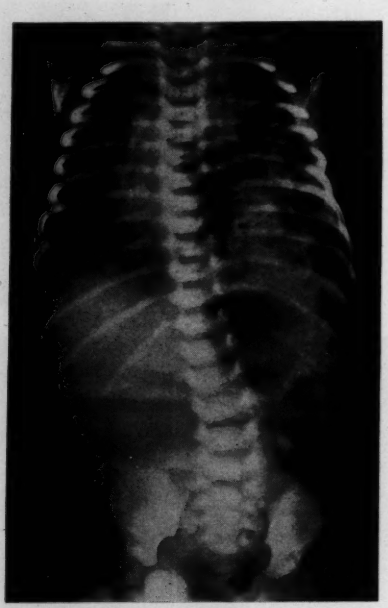

Fig. 24. *Congenital diaphragmatic hernia* through a large defect in the posterolateral portion of the left leaf of the diaphragm. Three week old female infant. Note small size of abdomen, and relative scarcity of air-filled bowel in abdomen.

of bowel are present in the chest. In severe cases the hernia may even occupy the entire hemithorax (Fig. 24). Air-fluid levels are often seen, and in these cases the roentgen picture may closely resemble that produced by congenital cystic lung disease or lung ectasias secondary to infection. If bowel obstruction is also present (malformation, kinks, volvulus or even pyloric stenosis), the loops may be greatly distended. The lung on the side of the lesion is variably compressed and often hypoplastic. The mediastinum may be displaced toward the opposite side. The abdomen is small, and there is often less air than normally seen. The diagnosis is in most cases obvious from the plain films of the chest and abdomen, as well as clinically. Barium studies[24] should be

undertaken only when the diagnosis is in doubt. Delayed films, after ingestion of a small amount of contrast material, are all that is necessary in such circumstances. The hernia may contain only a kidney, the spleen or part of liver (Fig. 25), omentum or colon, or may represent a transdiaphragmatic diverticulum or duplication of the alimentary

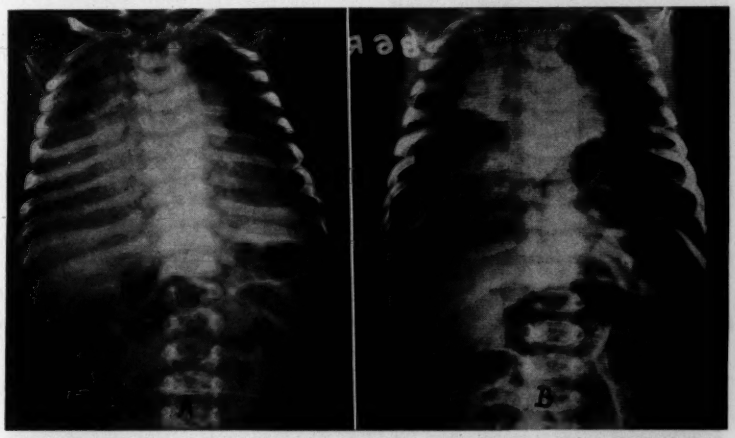

Fig. 25. *Congenital diaphragmatic hernia* through the retrosternal space. A, Large lobular mass in the anteroinferior mediastinum, which displaces the heart cephalad. The shadow normally supplied by the liver in the abdomen is deficient. *B*, Diagnostic pneumoperitoneum. The air outlines the herniated liver and the thin hernial sac. Male, 6 weeks.

tract. In these cases the roentgen findings in the plain films may only be those of a soft tissue water density mass in the thorax.

Paralysis and Eventration of the Diaphragm

Elevation of one leaf of the diaphragm, when of marked degree, may also give rise to respiratory embarrassment. The lung is compressed, and the mediastinum may be shifted.

Unilateral paralysis is due to phrenic nerve injury and commonly follows difficult delivery.[58] Brachial palsy on the same side is frequently present. The disease is more common on the right. At fluoroscopy the paralytic muscle moves paradoxically with respiration, and the mediastinal shadow may shift toward the normal side in inspiration.

Eventration is due to hypoplasia of muscle tissue and is more common on the left (Fig. 26). The diaphragmatic movements may be paradoxical; in approximately half of the cases they are said to be absent.[39]

Fig. 26. *Congenital eventration* of the left leaf of the diaphragm. At fluoroscopy the left dome of the diaphragm moved paradoxically, and the mediastinal shift toward the right was exaggerated in inspiration.

Diagnostic pneumoperitoneum[8] is sometimes necessary in the evaluation of diaphragmatic anomalies (Fig. 25).

Agenesis or Hypoplasia of Lung[25,45,48]

When an entire lung is absent or hypoplastic (Figs. 27, 28), roentgenographically there is marked to moderate diminution in the volume

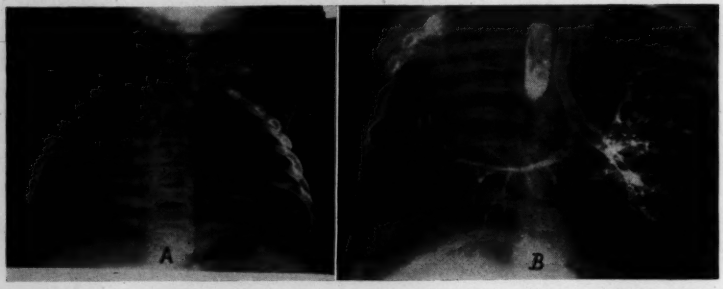

Fig. 27. *Agenesis of the right lung* in a male infant. *A*, Chest film at age 2½ months. The upper half of the right lung is diminished in volume and wholly opaque. The mediastinal shadow is shifted towards the right. Note cervical hemivertebra (arrow). *B*, Bronchogram at 11 months. Absence of right lung. Part of the left lung occupies the right lower hemithorax.

and air content of the affected hemithorax, and fluoroscopy reveals no or little local air exchange, according to the degree of severity of the malformation. The unaffected lung uniformly shows compensatory overexpansion, and the entire mediastinum is shifted toward the affected side. This compensatory emphysema may become obstructive if the major bronchus on the same side is for some reason distorted or compressed.[41] Similar findings in the plain films, and presumably also in the bronchograms, may be observed in the presence of a congenital complete bronchial web.[66] In this anomaly the lung distal to the obstruction is atelectatic, while the bronchi may be normal.

Bronchograms show complete absence of bronchi or only a rudimentary blind pocket filled with contrast material in agenesis of one lung. In hypoplasia, instead, the bronchi are diminutive and crowded together.

In agenesis and hypoplasia of one lobe, the roentgen findings of the affected areas are similar, but the emphysema of the remainder of the lungs and the respiratory symptomatology may be milder.

Congenital anomalies throughout the body, but especially in the vertebrae, are not uncommon in patients with lung aplasia or hypo-

Fig. 28. *Hypoplasia of the right lung* in 6 month old female infant.-A, Changes similar to those in Figure 27, A. *B*, Bronchogram. Hypoplastic bronchi on the right.

plasia. Vertebral anomalies in association with unusual lung changes should raise the question of maldevelopment of the lung.[5]

Congenital Stridor

Various types of congenital lesions, producing some degree of obstruction to the airways, may be responsible for noisy or embarrassed respiration from birth:[28, 29] choanal atresia; macroglosssia; glossoptosis; ranula; hygroma colli; cysts on the base of the tongue; tumors of the pharynx; goiter (Fig. 29); laryngeal anomalies, such as redundancy of the aryepiglottic folds, webs or stenoses, laryngeal cysts or tumors; tracheal stenosis; a tracheal web or cartilage bar; tracheomalacia and vascular rings singly or in combination; an aberrant left pulmonary artery compressing the trachea;[71] esophageal stenosis with dilatation of the proximal esophagus (Fig. 14); mediastinal masses and others. Laryngeal anomalies may be found in association with tracheo-esophageal fistula.[57] The concept that the thymus is responsible for stridor was discarded many years ago.

Many of these lesions can be demonstrated by relatively simple procedures, such as plain films of the chest and neck, and fluoroscopy with barium swallow. Cysts on the base of the tongue[61] and pharyngeal

tumors can be suspected in plain films and are easily outlined by swallowed contrast material. In all types of laryngeal obstruction, ballooning out of the hypopharynx in *inspiration* can be seen at fluoroscopy. Ballooning out of the hypopharynx in *expiration* is said to occur in choanal atresia.[68]

Fig. 29. *Hyperplastic goiter* in a 9 week old male infant. The tumor mass encircles the larynx.

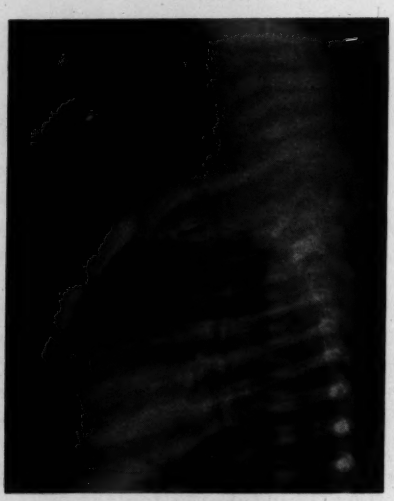

Fig. 30. *Tracheomalacia* in a 6 week old male infant. Note narrowing of trachea at the thoracic inlet (arrow).

Tracheal narrowing may be recognized in lateral films of the chest (Fig. 30). Vascular rings produce fairly characteristic compression defects in the walls of the esophagus.[19, 24] A Lipiodol tracheogram is at times indicated in the diagnosis of vascular rings and tracheomalacia. Undue tracheal collapse can be demonstrated if serial films are taken during the respiratory cycle.

Congenital Intrathoracic Masses

Intrathoracic masses[24] may be responsible for respiratory distress through compression or displacement of mediastinal structures, a major bronchus or lung tissue. The nature of the mass may be suspected preoperatively in many cases, but the final diagnosis often rests on the surgical and pathological findings. Bronchogenic cysts, duplication of the esophagus, diaphragmatic hernia, intrathoracic duplications of the alimentary tract, arising from the intestines and passing through a defect in the diaphragm, may present in this fashion. Air may be present in these masses. Neurogenic tumors such as neuroblastoma, ganglioneuroma, neurenteric cysts[27] and meningocele, herniating through an anterior defect in the vertebrae, present as posterior mediastinal masses. Dermoid cyst and teratoma must certainly be present in the newborn period, but we have had no personal experience with them in this age group. The recognition of an intrathoracic cystic hygroma is facilitated by the common extension of the mass into the neck. Fluid-filled lung cysts, congenital adenomatoid malformation of the lung in the early unaerated stage and nonair-containing pulmonary sequestration may present roentgenographically as intrapulmonary mass lesions.

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RESPIRATORY DISORDERS OF NEWBORN INFANTS

Correlation of Clinical and Pathological Observations

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Attempts to correlate clinical observations on infants with respiratory distress in the neonatal period with pathological observations in those who die have been rendered difficult (1) by the multiplicity of lesions which may be present in a single infant and may contribute to the overall clinical pattern, (2) by the relatively limited responses (or, in some instances, lack of response) of the newborn infant to a variety of stimuli, and (3) by the frequent lack of detailed pathological studies in infants dying during this period. This paper is offered in an attempt to correlate clinical and pathological observations in newborn infants dying with respiratory distress, and to present a classification of the various causes of respiratory disorders occurring in the newborn period which will be of practical assistance to the physician confronted with this problem.

In spite of the fact that approximately 5 per cent of all deaths occur during the neonatal period, the postmortem examination of newborn infants is all too frequently relegated to the newest, least experienced member of a Department of Pathology, who in effect serves an apprenticeship performing necropsies on newborn infants prior to being permitted to perform similar studies on adults. This is particularly unfortunate, since gross alterations comparable to those commonly associated with infections, neoplasia or degenerative disease in adults are usually absent. Since death certificates are completed prior to completion of histological study of the viscera, the pathologist is apt to attribute almost all neonatal deaths to the only obvious macroscopic abnormalities, viz., atelectasis and/or prematurity, neither of which is

for practical purposes an adequate primary cause of death. The obstetrician and pediatrician, finding that most deaths are attributed simply to atelectasis or prematurity, soon lose interest in attending necropsies and later make only a token effort to obtain permission for autopsy on infants dying shortly after delivery.

The lack of clinical-pathological cooperation in dealing with newborn infants is unfortunate, since there is probably no period of life during which clinical diagnoses are less exact and during which the clinician and pathologist could serve to such mutual advantage. The newborn infant responds to a variety of stimuli in a limited manner, and respiratory distress is the most common clinical problem with which the obstetrician and pediatrician are confronted. Many factors may be responsible for inhibiting the establishment of effective respiration or disturbing respirations when once established.

It can be argued that the descriptions of clinical patterns which follow are more definitive than is warranted. This oversimplification seems justified, however, since only by defining classic clinical patterns can these and variants thereof be recognized. Since more than one factor (e.g., anoxia, trauma and immaturity) may play a role in the production of respiratory difficulty in any given infant, this multiplicity of factors may result in atypical clinical manifestations and in the presence of multiple pathological findings. Nevertheless, recognition of the basic manifestations associated with each of the various factors concerned should aid in clarifying some, if not all, of the clinical patterns produced.

The terms "atelectasis," "prematurity," "abnormal pulmonary ventilation," "postnatal asphyxia with atelectasis" and "perinatal distress syndrome" are not included in the classification (Table 4). Prematurity is undoubtedly the single most important factor in most neonatal deaths, but is rarely and only in extreme instances the sole cause of death. Until adequate methods to prevent premature births are devised, attention must be directed to those factors in addition to immaturity which are immediately responsible for death. Atelectasis of varying degrees is almost constantly present in infants dying shortly after delivery. Complete postmortem examination, especially if augmented by a careful appraisal of the maternal record, will reveal the cause of persistent atelectasis in most instances, and thus atelectasis alone is not an adequate cause of death. Abnormal pulmonary ventilation,[6] postnatal asphyxia with atelectasis[7] and the perinatal distress syndrome[9] are descriptive terms with no single pathological basis. Use of such terms defeats attempts to define more specific causes of respiratory distress. Although they may contribute to our over-all knowledge of the processes responsible for respiratory distress and for death, such terms add little or nothing to exact clinical and pathological diagnoses. Moreover, such diagnoses obscure the fact that in a certain group of

infants the cause of respiratory distress and of death may not be demonstrable even after completion of the necropsy.

Clinical differentiation of respiratory disturbances of central and of pulmonary origin may be difficult or impossible. Lesions of central origin are characterized by apnea with infrequent, weak, irregular respiratory movements. The most frequent pulmonary lesion responsible

TABLE 4. *Causes of Neonatal Respiratory Disorders*

I. Lesions of the central nervous system
  A. Intracranial hemorrhage
    1. Intraventricular hemorrhage
    2. Subdural hemorrhage
  B. Fetal anoxia
  C. Congenital malformations
II. Pulmonary lesions
  A. Pulmonary hyaline membranes
  B. Pneumonia
  C. Pneumomediastinum and pneumothorax
  D. Pulmonary hemorrhage
  E. Congenital malformations
    1. Pulmonary hypoplasia
    2. Lobar emphysema
III. Miscellaneous
  A. Congenital malformations of heart and great vessels
  B. Paralysis of phrenic nerve
  C. Diaphragmatic hernia
  D. Esophageal atresia with tracheo-esophageal fistula
  E. Malformations of lower jaw, epiglottis or larynx

for respiratory distress (pulmonary hyaline membranes) is associated with dyspnea and with vigorous respiratory movements, as might be expected in the presence of an intact respiratory center.

INTRAVENTRICULAR HEMORRHAGE

Intraventricular hemorrhage occurs almost exclusively in the very small premature infant and often after an uncomplicated, atraumatic delivery. It accounts for approximately 10 per cent of neonatal deaths.[3] Clinical manifestations may be present at birth or may be delayed for several hours or even several days after delivery. During this latent period the infant may seem entirely normal or may appear somewhat hyperactive and unusually alert. The predominant clinical manifestations of intraventricular hemorrhage are respiratory, and death usually follows their appearance within a relatively short time. The infant is cyanotic, and the respirations are weak and irregular with periods of apnea. Other evidences of involvement of the central nervous system may be present and include irritability and loss of the Moro reflex. In a few instances intraventricular hemorrhage may occur in association with pulmonary hyaline membranes, and the clinical manifestations may be predominantly those of the latter condition.

At necropsy significant intraventricular hemorrhages are usually associated with subarachnoid hemorrhage in the cisterna magna, anterior surface of the pons, interpeduncular cistern and even in the region of the sylvian fissures. Small (and probably nonlethal) intraventricular hemorrhages often are confined to the occipital horns of the lateral ventricles and probably arise from the engorged vessels of the choroid plexus. Large intraventricular hemorrhages commonly arise from rupture of subependymal hemorrhages in the region of the terminal vein, between the caudate nucleus and the thalamus. It is these subependymal hemorrhages which probably account for the latent period which may be noted clinically. During the latent period blood accumulates within the "silent" subependymal zone, and only after the escape of blood into the ventricular system do clinical manifestations become apparent.

A variety of theories have been offered to explain the occurrence of subependymal and intraventricular hemorrhages. Mechanical trauma in the broadest sense of the term, anoxia with resultant vascular engorgment, and a "suction effect" produced as a result of high intrauterine pressure acting on the fetal body while the head is exposed to atmospheric pressure may play a role in their origin. The single most important factor, however, appears to be the immaturity of the infant, and thus they should not be considered traumatic in the usual obstetric sense and should not be attributed to obstetric mismanagement.

SUBDURAL HEMORRHAGE

Subdural hemorrhages of sufficient size to be responsible for clinical manifestations are usually traumatic in origin and are accompanied by tears of the dural septa. Although more frequently observed after long or difficult labor, breech delivery and delivery by midforceps, they may also occur after spontaneous, apparently atraumatic deliveries. Moreover, *the judicious use of low or outlet forceps may decrease rather than enhance the incidence of intracranial trauma.* Clinical manifestations are usually present at or shortly after birth, although less frequently they may be delayed for two or three days. The initiation of respiratory efforts by the infant is frequently delayed, and the respiratory movements are weak, irregular and gasping with periods of apnea and cyanosis. Signs and symptoms directly referable to the central nervous system include somnolence, loss of the sucking reflex, irritability, twitchings or frank convulsions, shock and a bulging fontanel. Retinal hemorrhages, which may be associated with subdural hematomas in older infants, are of no diagnostic significance in the newborn period. Spinal puncture frequently reveals red blood cells in the subarachnoid fluid, but the presence or absence of blood neither confirms nor excludes the presence of subdural hemorrhage. The diagnosis can be confirmed clinically only by subdural taps with the demonstration of blood in the

subdural space. In some instances the usual taps performed through the coronal suture fail to reveal evidence of hemorrhage. If clinical evidence favors the presence of subdural hemorrhage, the taps should be repeated through the lambdoidal sutures.

Postmortem examination reveals blood spread diffusely over one or both cerebral hemispheres. The bleeding is often accentuated on the superior surface of the leaves of the tentorium cerebelli, and therefore estimation of the amount of subtentorial hemorrhage may be rendered difficult by inadequate cleansing of this area and improper removal of the brain stem and cerebellum. Hemorrhage in the subtentorial space is particularly significant, since many important structures are here enclosed within a relatively small space. Small amounts of subdural hemorrhage may be anoxic in origin and not associated with tears of the dural septa. Larger traumatic subdural hemorrhages are usually associated with tears of one or both leaves of the tentorium cerebelli or less frequently of the falx cerebri. The tears of the tentorium are usually incomplete; i.e., they do not completely penetrate the fibers of the tentorium. They are usually located just posterior to the free edge of this structure. Tears of the dural septa may be encountered in the absence of subdural hemorrhage and are not by themselves responsible for clinical manifestations; probably many infants survive with no untoward effects after sustaining tentorial tears in the newborn period. Such tears are indicative of increased intracranial stress, but it is the associated hemorrhage which is responsible for clinical manifestations and for death. Subdural hemorrhages occurring during delivery are not encapsulated, and their relation (if any) to the subdural hematomas encountered in older infants is not clearly established.

Subarachnoid hemorrhages are predominantly anoxic and not traumatic in origin. Small amounts of subarachnoid hemorrhage are common after delivery and usually are not associated with clinical manifestations. Large subarachnoid hemorrhages are usually secondary to intraventricular hemorrhage, and involve especially the basilar cisterns. Large subarachnoid hemorrhages occurring independently of intraventricular hemorrhage are rare and play a minor role in the origin of respiratory disorders in the newborn. In like manner large intracerebral hemorrhages (exclusive of those in the subependymal zone) are rare findings at postmortem examination of newborn infants. *"Intracranial hemorrhages" responsible for clinical manifestations in the newborn infant are usually subdural or intraventricular in location.*

FETAL ANOXIA

Fetal anoxia is one of the most important causes of respiratory difficulty in the newborn infant. For proper interpretation of both clinical and pathological findings the maternal history must be carefully

analyzed, since a variety of factors may be responsible for impairment of the supply of oxygen to the fetus. Hypoxia may be produced by such conditions as abruptio placentae, placenta previa, placental insufficiency from whatever cause, compression of the umbilical cord, prolonged labor or maternal hypotension such as may occur as a complication of spinal anesthesia. If the hypoxia is sufficiently severe, the fetus is stillborn. Depression of the fetal heart rate or the presence of amniotic fluid stained with meconium (except with breech presentations) should alert the physician to the possibility of intrauterine death or of neonatal difficulty secondary to hypoxia. If the infant is liveborn, there is usually delay in the initiation of respiration, and after respiratory efforts have been established they are gasping in type, weak, irregular and ineffectual with periods of apnea. The infant is cyanotic, somnolent, hypotonic or hypertonic, and the sucking reflex is poor. If death occurs as a result of uncomplicated fetal anoxia, it usually does so in utero or within 24 hours after delivery; in those infants surviving longer periods of time, complications such as pneumonia may intervene. Although there is clinical, experimental and pathological evidence to indicate that periods of prolonged hypoxia may produce permanent cerebral damage, attempts to predict the presence or absence of subsequent cerebral damage on the basis of the occurrence of apnea[14] or upon the oxygen content of the neonatal blood[2] are highly unreliable.

Postmortem examination of infants dying as a result of fetal anoxia commonly reveals atelectasis, visceral congestion and the presence of multiple petechiae involving especially the pleural and pericardial surfaces and the thymus. However, these macroscopic alterations are commonly present in infants dying of a variety of causes during the neonatal period. We have therefore confined the pathological diagnosis of fetal anoxia to those infants in whom histological examination of multiple sections of lung reveals the presence of large amounts of amniotic debris in the pulmonary air spaces. Small amounts of cornified debris are encountered in the lungs of many infants dying of a variety of causes during the neonatal period and should not be considered indicative of intrauterine hypoxia. Repeated deep intrauterine respiratory movements with resultant aspiration of large amounts of cornified debris do not occur under normal circumstances. There is general agreement that the presence of abundant amniotic debris in the pulmonary air spaces is indicative of fetal anoxia. Other elements, especially meconium, may be encountered less frequently. *Instances of acute severe intrauterine anoxia may occur in the absence of excessive aspiration of amniotic debris,* and thus complete reliance should not be placed on pathological findings alone.

Note that fetal anoxia is included among the causes of respiratory disorders of central origin and that the clinical manifestations are often

similar to or indistinguishable from those associated with intracranial trauma with subdural hemorrhage. Pathological alterations in the central nervous system of infants dying as a result of fetal anoxia are usually minimal or absent, probably because of the rapidity with which death ensues. Aspiration of amniotic fluid and its constituent cornified epithelial cells probably only rarely produces respiratory embarrassment, the fluid being rapidly absorbed and the epithelial elements producing only a mild, delayed response characterized by a slight infiltration of macrophages; rarely they may produce some degree of obstruction. Thus, although the classic morphological alterations associated with fetal anoxia are located in the lungs, respiratory distress and death result from damage to the central nervous system rather than from primary pulmonary failure.

CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

No attempt will be made to discuss the variety of congenital malformations of the central nervous system which may be encountered in the newborn period, and which, if sufficiently severe, may give rise to respiratory disorders of central origin. The more obvious malformations, e.g., severe hydrocephalus and anencephaly, present no diagnostic problem. Severe malformations of the brain may occur, however, with no apparent external evidences, and in some instances delayed onset of respiration with subsequent weak, irregular respiratory movements may dominate the clinical picture in the early days of life. More definite evidences of cerebral damage may not be apparent until several weeks or months of age, and at that time review of the neonatal history may lead to the conclusion that the injury to the central nervous system was sustained as a result of anoxia or trauma during delivery. Although permanent damage to the brain may occur during this period, it is important to recall that respiratory disorders in the newborn infant may also be the result of pre-existing malformations of the brain.

PULMONARY HYALINE MEMBRANES

Probably no lesion encountered in the newborn period has received such notoriety in recent years, nor such adverse criticism as both a clinical and pathological entity, as has the condition referred to as pulmonary hyaline membranes. Recognition of the occurrence of nonlethal examples of hyaline membranes, combined with incomplete knowledge of the pathogenesis of the condition, has led to a reluctance to accept it as an entity, and it has been included with other clinical and pathological processes in such categories as abnormal pulmonary ventilation, postnatal asphyxia with atelectasis and the perinatal distress syndrome.

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Admittedly, the use of too broad clinical and pathological criteria for the diagnosis of pulmonary hyaline membranes will result in its use as a diagnostic "wastebasket," with no advance in knowledge over that associated with such diagnoses as atelectasis and prematurity. Not all infants with respiratory distress have pulmonary hyaline membranes, and the simple presence of a few such membranes in the lungs at necropsy does not serve as an adequate explanation for respiratory distress. However, a relatively constant clinical pattern of respiratory distress is associated with relatively constant pathological findings which can, in the majority of instances, be correctly predicted by the clinician prior to postmortem examination. This, then, would appear to represent an entity, despite our present ignorance of its pathogenesis or the exact mechanism by which clinical manifestations are produced. The exact role of pulmonary hyaline membranes in neonatal mortality will be evaluated properly only by careful appraisal of the total clinical and pathological data.

Pulmonary hyaline membranes are now the single most frequent significant pathological finding in premature infants dying during the early neonatal period. They occur far more frequently but not exclusively in premature infants and are more likely to be encountered in infants delivered by cesarean section and in infants born of diabetic mothers than in others. Clinical manifestations may be present at birth or may be delayed for a few hours after delivery. The signs and symptoms are those of labored respiratory efforts with increasing cyanosis, dyspnea and respiratory grunt. Retraction of the suprasternal region and of the lower thoracic border becomes increasingly severe. The respiratory efforts are not unlike those seen in older infants with obstructive bronchiolitis, and are in striking contrast with the weak respiratory movements of the infant with depression of respiration on the basis of damage to the central nervous system. As the respiratory difficulty increases in severity, auscultation of the chest reveals poor air exchange in spite of the vigorous respiratory movements. Roentgenographic examination initially reveals a fine granular reticular pattern throughout both lungs which finally becomes confluent with extensive opacification of the lungs. Clinical evidence would suggest that many infants with pulmonary hyaline membranes recover. In those infants who die without complications, death usually occurs within 24 to 48 hours after delivery. Infants dying later commonly have some complication such as pneumonia or less frequently pneumomediastinum and pneumothorax.

At postmortem examination lungs containing pulmonary hyaline membranes are commonly deep purplish red and noncrepitant, but the macroscopic appearance is not pathognomonic, and an unequivocal diagnosis should be made only by histological examination. Histological

sections reveal extensive atelectasis with approximation of adjoining interalveolar septa and a resultant *apparent* increase in the width of the interalveolar septa. There is intense congestion of the interalveolar capillaries, and a number of the alveolar ducts, alveoli and respiratory bronchioles are lined by acidophilic, homogeneous or granular membranes. Additional findings such as aspiration of amniotic debris, intra-alveolar hemorrhage, pneumonia and interstitial emphysema may be present in some but not all instances. Their significance in the production of respiratory symptoms, as well as that of extrapulmonary lesions such as intraventricular hemorrhage which may be encountered in some infants, must be evaluated by the severity of the various lesions and by a careful appraisal of the clinical manifestations. The simple presence of a few thin membranes lining scattered alveolar ducts should not be considered adequate to explain death as a result of respiratory embarrassment, and the triad of atelectasis, congestion and acidophilic membranes should be present in some degree of severity before death is attributed to pulmonary hyaline membranes.

A number of theories have been advanced to explain the presence of pulmonary hyaline membranes in newborn infants.[15] Aspiration of amniotic fluid,[4] transudation of protein from pulmonary capillaries resulting from capillary damage[3] or cardiac failure,[12] oxygen poisoning[5] and the action of thromboplastic substances in amniotic fluid acting upon edema fluid within the lungs[8, 11] have all been suggested as possible mechanisms responsible for the development of these membranes. Suffice it to say that there is still no unanimity of opinion concerning their origin, and that any postulated mechanism of development must explain (1) the nature of the membranes, (2) their occurrence predominantly in premature infants and in infants born by cesarean section, (3) their occurrence in infants born of diabetic mothers, (4) the mechanism responsible for the associated atelectasis and congestion, and (5) the relation between these membranes and those encountered in older infants, children and adults. Only when these problems are solved will real advances be made in significantly reducing neonatal mortality in this large group of infants.

PNEUMONIA

Pneumonia may occur as a primary lesion or as a complication of other lesions responsible for respiratory difficulty, e.g., anoxia, cerebral trauma or pulmonary hyaline membranes. Its exact incidence at this time is not known. As recently as 1947 it was recorded as being responsible for 10 per cent of neonatal deaths, and was present as a contributory rather than as a primary cause of death in an additional 25 per cent of infants dying during the neonatal period;[3] possibly its inci-

dence may now be somewhat lower, but this fact is not established. Pneumonia may be contracted in utero or early postnatal life, and differentiation of intrauterine and postnatal pneumonia may be impossible.

A variety of organisms may be responsible for infections in the newborn period, but gram-negative bacilli and staphylococci are certainly among the most important and must be considered in the choice of antibiotic therapy.

Clinical manifestations of pneumonia occurring as a complication of other lesions responsible for respiratory distress are often completely obscured by the underlying process. Thus postmortem examinations of infants dying as a result of fetal anoxia or pulmonary hyaline membranes (especially in those infants surviving beyond 24 to 48 hours) frequently reveal histological evidence of pneumonia not suspected during life. Any infant with a history of premature rupture of the fetal membranes, of a prolonged or difficult labor or with a history indicative of fetal anoxia, as well as any infant with clinical manifestations suggesting the presence of pulmonary hyaline membranes, should receive suitable antibiotic therapy prophylactically. The presence of pneumonia complicating other respiratory disorders may be suspected, but is usually not diagnosed with certainty during life.

Pneumonia uncomplicated by other pathological processes is extremely difficult to diagnose. The symptoms are usually not characteristic and are not predominantly respiratory. The initial manifestations are often listlessness and refusal to nurse. Weight loss, increase and irregularity in the respiratory rate and a poor color to the point of true cyanosis may be noted later. Costal retraction is minimal or absent, in contrast to infants with pulmonary hyaline membranes, and cough is almost never present. In some infants cerebral manifestations may be prominent with flaccidity or hypertonicity and with twitchings or frank convulsions. Fever is usually absent, but may be present, especially in full term infants. Physical examination may reveal no abnormal findings, or there may be areas of dullness, decreased breath sounds and rales; as in other pulmonary lesions in the early neonatal period, interpretation of the physical findings may be extremely difficult. Roentgenologic findings have been reported only infrequently, but areas of consolidation, scattered opacities and diffuse clouding of the lungs have been observed in some instances.[13] The roentgenological findings must be interpreted with caution, and it seems probable that roentgenological abnormalities may be entirely absent. Positive blood cultures may be obtained in some instances, and the results of nasopharyngeal cultures may aid in the selection of proper antimicrobial therapy.

As in other infections in the newborn, the signs and symptoms of pneumonia are often not striking and may be entirely overlooked if those in charge of the infant's care are not alert to minor changes in his

behavior. If the infection is extremely severe and overwhelming, the infant may be found dead without previous warning symptoms.

At postmortem examination the diagnosis of pneumonia is made almost exclusively by histological examination of multiple sections of lung. Macroscopic changes in the form of pleuritis or recognizable areas of consolidation are usually absent except in staphylococcal pneumonia, in which multiple hemorrhagic areas of consolidation with central necrosis and abscess formation may be present in addition to empyema or pyopneumothorax.

Histologically, the diagnosis of pneumonia is dependent upon demonstration of an exudate of neutrophils in the pulmonary air spaces; numerous mononuclear cells suggesting macrophages or alveolar septal cells are frequently encountered in the alveoli of infants dying a few days after delivery, and are not interpreted by us as evidence of pneumonia.

It is apparent that the clinical diagnosis of pneumonia in the newborn infant is often difficult or impossible. Only by recognition of its frequency will adequate prophylactic therapy and early diagnoses be established. Hopefully, a certain number of needless deaths may thus be prevented.

PNEUMOMEDIASTINUM AND PNEUMOTHORAX

Interstitial pulmonary emphysema results from the rupture of alveolar walls with extension of air into the subpleural and interlobular septa. From here the blebs of air may extend along the vascular sheaths into the mediastinum (pneumomediastinum) and subsequently even into the subcutaneous tissue. Rupture of mediastinal blebs or probably less frequently direct rupture of a subpleural bleb results in pneumothorax. The rupture of alveolar septa may be caused by any lesion responsible for hyperdistention of the air spaces. It may occur after injudicious attempts at resuscitation or may be associated with partial obstruction such as may occur with pulmonary hyaline membranes, with excessive aspiration of amniotic debris or with pneumonia. Mild degrees of pneumomediastinum and pneumothorax are probably more common than is generally appreciated and may cause no respiratory embarrassment. Large accumulations of air in the pleural space may be responsible for the sudden onset of respiratory embarrassment with dyspnea and cyanosis. Physical examination reveals limitation of movement of the chest on the affected side, displacement of the heart to the opposite side and depression of the diaphragm; with a right-sided pneumothorax the downward displacement of the liver may simulate hepatomegaly. Auscultation reveals diminished or absent breath sounds, and the percussion note is hyperresonant; with bilateral pneumothorax diag-

nosis by physical examination may be difficult because of the similarity of findings on the two sides. Extensive pneumomediastinum may cause bulging of the sternum and distention of the veins of the neck. The diagnosis of pneumothorax and/or pneumomediastinum is established by roentgen examination of the chest; both anteroposterior and lateral views should be taken. If severe respiratory embarrassment is present, it may be relieved by aspiration of the air.

In order to confirm the presence of pneumothorax at necropsy the pleural cavities should be opened under water. Minor pneumothoraces will be overlooked if this is not done, and the diagnosis of even large accumulations of air in the pleural space may remain in doubt.

PULMONARY HEMORRHAGE

Massive intra-alveolar hemorrhage may occur in infants dying within a few hours after delivery, probably the result of fetal anoxia. More frequently extensive intra-alveolar hemorrhage is encountered in infants living a few days and is seen classically in those with kernicterus, in whom the terminal event is often the passage of a large amount of frothy blood from the nose and mouth. Still other infants without kernicterus, and often with no evidence of pre-existing disease, may have massive intra-alveolar hemorrhage associated with blood in the nose and mouth, vomiting of blood and dullness and rales in the chest; these manifestations may precede death by several hours.[1] Hypoprothrombinemia, anoxia, cerebral damage and infection have all been suggested as etiological agents, but no single factor appears to be uniformly responsible.

PULMONARY HYPOPLASIA

Bilateral pulmonary hypoplasia is usually associated with other congenital malformations, e.g., anencephaly, bilateral renal agenesis and polycystic disease of the kidneys. Infants with diaphragmatic hernias have failure of complete development of the lungs, the lung on the affected side being especially involved. After successful surgical repair of the diaphragmatic defect and the resultant production of adequate thoracic space the lungs ultimately assume a normal appearance. Unilateral pulmonary agenesis is compatible with life. It is often associated with the presence of hemivertebrae. The contralateral lung is hyperexpanded and may partially fill the opposite pleural cavity.

LOBAR EMPHYSEMA

Severe emphysema of a single lobe is an uncommon cause of respiratory distress[10] in infants and is not usually encountered until after the

immediate neonatal period. The infants are in apparent good health until the onset of respiratory symptoms; there is no evidence that trauma, infection or aspiration of foreign materials plays any role in the development of the emphysema, and the evidence strongly favors a congenital rather than an acquired lesion. The onset of clinical manifestations is usually sudden with severe dyspnea and cyanosis. The physical, roentgenographic and fluoroscopic findings are those of severe emphysema localized to a single lobe. The cause of this lesion is not known, although a variety of theories have been suggested. Lobectomy is usually followed by relief of symptoms, and the lesion may be fatal in the absence of surgical intervention.

MALFORMATIONS OF THE HEART AND GREAT VESSELS

Dyspnea, stridor, cough, mild cyanosis, repeated respiratory infections and dysphagia may sometimes result from malformations of the great vessels producing vascular rings, but these are not a frequent cause of significant respiratory distress in the early newborn period. Cyanotic types of congenital malformations of the heart, e.g., transposition of the great vessels, tricuspid atresia and truncus arteriosus, may produce intense cyanosis with some increase in respiratory rate during the neonatal period. Differentiation of congenital heart disease and other causes of cyanosis may be difficult during this period. Transitory murmurs may be present in newborn infants without cardiac lesions, and severe cardiac malformations may not be responsible for a murmur. Roentgenographic studies often reveal no evidence of cardiac enlargement or abnormal configuration during the first few days of life. True respiratory distress in the form of grunting respirations or costal retractions is usually absent in spite of the increased respiratory rate, but periods of apnea may be present in some instances. Crying and exertion often intensify the cyanosis associated with congenital cardiac malformations, whereas they may somewhat alleviate that present with pulmonary or even intracranial lesions. The cyanosis associated with congenital cardiac malformations responds somewhat less readily to the administration of oxygen than does that associated with poor pulmonary function based on other causes. In some instances an unequivocal diagnosis of congenital heart disease can be established only after several days, when recovery from other conditions responsible for persistent cyanosis usually occurs. During this period more definitive clinical and roentgenographic evidences of cardiac malformations will often become apparent.

PARALYSIS OF PHRENIC NERVE

Injury to the phrenic nerve with consequent diaphragmatic paralysis results from injury or even avulsion of the cervical nerve rootlets and is

usually associated with brachial palsy. Such injuries usually occur when delivery of the shoulder is difficult and traction on the head produces damage to the nerve rootlets. Clinical manifestations are those of respiratory distress with cyanosis and rapid respiration. Physical examination reveals decreased breath sounds on the affected side and absence of abdominal movements with inspiration. The diagnosis is readily confirmed by fluoroscopic examination; the diaphragm is elevated on the side of the injury, and the two leaves of the diaphragm move in opposition during respiration (seesaw movements). Recovery usually occurs, but intercurrent pneumonia is an important complication and may be responsible for death.

DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernias occur more commonly on the left side. There may be partial or complete absence of the diaphragm on the affected side. Large defects usually give rise to clinical manifestations soon after birth. These include severe respiratory distress with dyspnea, cyanosis and sometimes evidence of intestinal obstruction such as vomiting. The abdomen is scaphoid, and there are diminished respiratory movements of the chest on the affected side. Percussion reveals dullness or tympany, depending upon the presence of solid viscera or of hollow viscera containing fluid or air. The heart is displaced to the opposite side. Auscultation reveals diminished or absent breath sounds, and intestinal sounds may be audible.

The diagnosis may be established roentgenographically without the use of a contrast medium by demonstration of loops of bowel in the affected side. If a contrast medium is needed, material other than barium should be used. In some instances replacement of the viscera into the abdominal cavity and surgical repair of the diaphragmatic defect are possible. In others the degree of pulmonary hypoplasia is incompatible with life.

The defects involve especially the posterolateral aspect of the diaphragm, and parts of the stomach, liver, intestine and the entire spleen are commonly present in the thoracic cavity on the affected side.

ESOPHAGEAL ATRESIA WITH TRACHEO-ESOPHAGEAL FISTULA

Atresia of the esophagus is usually associated with a fistulous communication between the trachea and esophagus, most frequently with the distal segment of esophagus. Less frequently a tracheo-esophageal fistula may occur in the absence of esophageal atresia. In the usual form of esophageal atresia the first manifestation is the presence of excessive secretions of mucus in the mouth. This is followed by prompt regurgitation through the nose and mouth of every feeding.

Attacks of choking and cyanosis follow aspiration of the regurgitated material, and pneumonia soon develops. The diagnosis is confirmed by inability to pass a catheter into the stomach and by the use of a contrast medium to outline the proximal esophageal pouch; iodized oil should be used because of the danger of aspiration of barium into the lungs. The presence of air in the stomach confirms the existence of a fistulous tract between the tracheobronchial tree and the distal esophageal segment. Early diagnosis and surgical correction are necessary to prevent death.

MALFORMATIONS OF THE LOWER JAW, EPIGLOTTIS OR LARYNX

Severe hypoplasia of the mandible is commonly associated with posterior displacement of the tongue and results in respiratory difficulty and cyanosis. Supraglottic or laryngeal webs and obstruction of the infraglottic region by cartilage are rare causes of stridor and respiratory difficulty in the newborn period.

Abnormalities of the epiglottis and aryepiglottic folds may be associated with laryngeal stridor. Symptoms are usually absent at birth, but begin in the first week of life and are characterized by inspiratory stridor and retraction of the suprasternal and infrasternal regions. Cyanosis and dyspnea usually appear only with crying and exertion. Spontaneous recovery usually ensues after a year or sometimes longer. The abnormalities are demonstrable by direct laryngoscopic examination, but in infants who die of other causes distinct morphological changes in these structures are usually absent.

Paralysis of the vocal cords may be unilateral or bilateral and is usually associated with trauma incurred at birth. Severe dyspnea and stridor are associated with bilateral paralysis and often necessitate tracheotomy.

SUMMARY

Various causes of respiratory disorders in the newborn period are discussed, and the clinical observations are correlated with pathological findings.

The most common types of intracranial hemorrhage responsible for respiratory disturbances in newborn infants are intraventricular and subdural. Intraventricular hemorrhages occur predominantly in very small premature infants and are not the direct result of trauma. Subdural hemorrhages of sufficient magnitude to produce clinical manifestations are traumatic in origin and are associated with tears of the dural septa. Fetal anoxia produces clinical manifestations on the basis of cerebral damage, although morphological changes in the central nervous system in infants dying shortly after birth are minimal or absent.

Pulmonary hyaline membranes constitute an important clinical entity, especially in premature infants. The mechanism responsible for their production is not known. They are associated with dyspnea and vigorous respiratory efforts, in contrast to the weak, irregular respiratory movements with periods of apnea characterizing lesions of central origin.

Pneumonia is a frequent primary and contributory cause of neonatal deaths. It may be associated with other lesions responsible for respiratory distress or may occur independently. The clinical diagnosis is extremely difficult, and the pathological diagnosis is dependent upon histological examination.

A variety of other lesions responsible for respiratory disorders in the newborn period are briefly discussed.

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BACTERIAL PATHOGENS OF THE RESPIRATORY TRACT OF THE NEWBORN INFANT

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The development of the normal bacterial flora in the upper respiratory tract of newborn infants has been the subject of remarkably few careful bacteriological investigations. Yet a good understanding of the normal flora is obviously basic to any definition of "pathogens." Nor have studies to date yielded clear-cut information as to whether the initial flora of the newborn is acquired from the birth canal during parturition or from contact with adults after birth. The data of Solomon,[12] of Witkowski[19] and of Schweitzer[14] suggest that the oral cavity does not remain sterile for more than a few hours after birth, and that the bacteria to be found there in the earliest hours of life are the nonhemolytic streptococci and the coliforms acquired from the vaginal canal of the mother. On the other hand, Gundel and Schwartz[8] found the mouth sterile six hours after birth in 37.5 per cent and the nose in 42.5 per cent of 40 infants tested. Torrey and Reese[18] found that the nasopharynx and throat of infants 24 hours old yielded sterile cultures in almost all cases, and that even after 48 hours 12.5 per cent of the cultures were sterile. These figures agree well with those of Kneeland[9] and of Smith and Bloomfield.[15] Whereas Torrey and Reese[18] found white staphylococci, alpha and gamma streptococci and diphtheroids to be the earliest invaders of the respiratory tract even in nursing infants whose mothers were carriers of pneumococci and other pathogens, Witkowski[19] found heavy growths of *Escherichia coli* by the second day in 40 per cent of 50 infants; Solomon's experience was similar.[17] Cornelison, Johnson and Fisher[3] found an increase in positive cultures at the time of birth dependent directly on the time between rupture of the membranes and birth of the infant; also they found *E. coli* in

11 per cent of the infants examined. Investigations by Franklin and Loeb[7] probably have some bearing on the problem: they compared cultures of the eyes of the newborn at the time of delivery with postpartum uterine cultures and found in both cases a flora consisting predominantly of staphylococci, streptococci and *E. coli*. That the vaginal flora is not without importance to the infant was shown in the case of a nonbacterial pathogen by Anderson, Sage and Spaulding,[1] who made a comparative study of vaginal swabs of mothers and mouth swabs of infants with respect to *Candida albicans:* when the mother's swab was positive, the onset of clinical signs of thrush was within three days; but if the mother's swab was negative, the onset was delayed.

These data suggest that the oropharynx of the healthy newborn is, under the conditions of best obstetrical asepsis, sterile at birth, the initial flora being then acquired from the environment after birth; with less than ideal conditions the flora of his upper respiratory tract will be derived from the flora of the mother's vaginal canal and will consist of staphylococci, alpha and gamma streptococci, diphtheroids and, to a variable degree, coliforms.

The next question of interest is when the newborn acquires the nasopharyngeal microorganisms considered pathogenic for older persons. Torrey and Reese[18] studied a group of 105 full term breast-fed infants and their mothers and compared their respective nasopharyngeal floras. Their observations indicate that the upper respiratory tract during the first two weeks of life rarely becomes infected with *Diplococcus pneumoniae, Streptococcus pyogenes,* and *Hemophilus influenzae* even through contact with nursing mothers who are carriers of these organisms. The upper respiratory tract of the newborn does not appear to provide adequate conditions for growth of these pathogens. Entirely different is the situation with respect to *Staphylococcus aureus*. Torrey and Reese[18] recovered coagulase-positive strains of this organism from 9.5 per cent of their 105 infants on the first day; from 50 per cent after the second day, and from 90 per cent between the fourth and the eighth days, and concluded that the nose of the newborn provides a much more favorable medium for the growth of this organism than is the case in the adult. Cunliffe,[4] following the process day by day in a maternity hospital, found that 96 per cent of infants were carriers by the second week of life, with a rather sharp fall in the ensuing months.

Dancis, Grobow and Boyer[5] have put forth the interesting suggestion that the high level of salivary chlorides in infancy, together with the ability of the staphylococcus to grow at high salt concentrations,[10] may account for the presence of staphylococcus in the nasopharynx of the newborn more or less to the exclusion of other recognized pathogens of older infants and adults.

It should not surprise us, then, that in recent years the epidemiological spread of antibiotic-resistant staphylococci should have given rise to particularly serious problems among newborn infants.[12]

As for the source of the staphylococci in the infant, present evidence seems to exonerate the mother in most cases. The data of Barber, Hayhoe and Whitehead,[2] of Cunliffe[4] and more recently of Edmunds and his co-workers[6] show that the mother's organism is usually of a different specific type from that present in the infant, and that strains isolated from infants resemble those from members of the staff and not those obtained from their mothers.

Though the upper respiratory tract of the newborn provides a favorable growth medium for the staphylococcus, the same cannot be said of the lower respiratory tract. In a recent postmortem study of the causes of death in newborns by Rohmer and his co-workers,[13] bacteriological investigations of the respiratory tract revealed coliforms, enterococci, Klebsiella, Pseudomonas, Proteus, Salmonella and Staphylococcus in the throat and lower respiratory tract; however, Staphylococcus was present only six times among 26 infants dead of pneumonia, and never alone, whereas coliform bacteria were present in every case.

The prophylactic implications of these data are clear-cut so far as the importance of obstetrical asepsis is concerned, not only for the sake of the mother's well-being, but also for the prevention of infections in the newborn infant, particularly of infections due to coliform microorganisms, which are likely to cause pneumonia as well as sepsis.[16] The problem of controlling the spread of staphylococcal infection among newborn infants remains at present unsolved. Nor is there any unanimity of opinion regarding routine administration of antimicrobial drugs to all infants within a nursery for premature or newborn infants.

On the basis of these considerations it would seem reasonable to recommend antimicrobial drugs for all premature and newborn infants of mothers whose membranes ruptured unusually early in labor, and for all prematures born under circumstances in which obstetrical asepsis was inadequate. In such situations drugs effective against coliform organisms should be used: Aureomycin, Terramycin, chloramphenicol, streptomycin or the sulfonamides.

Respiratory infections developing in infants of more than three or four days of age are usually due to infection[13] either with coliform organisms, with other gram-negative bacilli or with penicillin-resistant staphylococci. Under these circumstances one of the antimicrobial drugs, or a combination of them, would seem to be indicated. Penicillin should probably be reserved for infections due to strains of staphylococcus proved sensitive to the drug.

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ANOMALIES OF THE RESPIRATORY TRACT

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CLINICAL SIGNIFICANCE

Malformations of the respiratory tract may have clinical significance for one or several reasons:

1. They may cause dyspnea, cyanosis, stridor or other manifestations of respiratory distress. The condition may be mild or so severe as to cause death by asphyxia, and the manifestations may be constant or intermittent. If the latter, they are often aggravated by feeding, crying or other exertion. Malformations of the respiratory tract causing respiratory distress must be distinguished from infectious processes, congenital heart disease, central nervous system disease, neoplasms of the neck and thorax, and other causes of respiratory difficulty.

2. Malformations may predispose the patient to, enhance the severity of, or perpetuate, infection of the air passages. They must then be differentiated from foreign bodies and other obstructive lesions, from asthma and other allergic disorders and from infectious processes such as bronchiectasis, lung abscess, tuberculosis and mycosis. Also to be distinguished from such malformations are a variety of metabolic and other disorders leading to repeated or chronic respiratory tract infection, including hypogammaglobulinemia, fibrocystic disease of the pancreas, familial dysautonomia (Riley syndrome), mongoloid idiocy, and gargoylism.

3. Malformations may, particularly if not recognized, confuse the interpretation of radiologic studies and may complicate surgical procedures. Those associated with anomalous vascular supply may lead to

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death from hemorrhage when the anomalous vessel is severed accidentally.

4. Respiratory tract malformations may suggest the existence of other malformations, both in the respiratory tract and in other parts of the body. Conversely, certain anomalies of other sites should direct attention to the possibility of malformation of the respiratory tract.

5. Malformations may cause genetic and eugenic problems to be presented to the physician, such as the chance of occurrence of the malformation in subsequent children, the risk for children of an affected parent or for children of unaffected parents whose pedigrees show the disease.

FREQUENCY

With the exception of cleft palate, tracheo-esophageal fistula and diaphragmatic hernia, no clinically significant anomalies of the respiratory tract can be considered common. In the detailed study by Murphy,[79] for every 10,000 live births there were 47 infants who died with malformations (0.47 per cent of live births), but anomalies of the respiratory tract comprised only 0.3 per cent of all malformations. Other series have demonstrated a similar rate of occurrence.[38, 79, 104] Selected data from three studies, giving the frequency of several respiratory tract anomalies in terms of live births, stillbirths and neonatal deaths, and malformed individuals, are presented in Table 5. Additional data on the frequency of cleft palate are given on page 77.

TABLE 5. *Incidence of Respiratory Tract Anomalies in Terms of Live Births, Stillbirths, Neonatal Deaths and Malformed Individuals*

	HARRIS AND STEINBERG[38] (Liveborn infants, 8716)	MC INTOSH ET AL.[75] (Stillbirths and neonatal deaths, 219)	MURPHY (1954) (Malformed persons, 935)
Harelip and/or cleft palate	46		
Harelip with cleft palate	6		
Cleft palate alone	3		
Diaphragmatic hernia	1	3	7
Tracheo-esophageal fistula	3		3
Hemangioma of larynx	1		
Atresia of larynx		1	
Anomalous lung lobation		1	
Malformation of epiglottis			1
Tracheal stenosis			1
Bronchial stenosis			1

NOSE, NASAL PASSAGES, NASOPHARYNX AND NASAL ACCESSORY SINUSES

Nose

The cylindrical, proboscis-like or otherwise malformed nose of *cyclopia* does not communicate with the nasopharynx, and in some victims there may be respiratory difficulty analogous to that of choanal atresia. What appears to be a milder form of the cyclopic state is *cebocephaly;* these patients have hypoplasia of the maxillary bones and nose, and fusion of the cerebral hemispheres with internal hydrocephalus and agyria (lissencephaly).[87] The writer has observed cleft palate in such patients. Similar brain lesions have been reported[36a] in patients considered to have *mandibulofacial dysostosis,* and a sequence of allied disorders, from cyclopia through cebocephaly to mandibulofacial dysostosis, may actually exist. Partial or complete duplication of the nose (rhinodymia) may occur in association with *anencephaly,*[13 87] but, as with cyclopia, symptoms due to the nasal malformation are of little significance. The broad turned-up nose of *hypertelorism* and the pug nose of *achondroplasia* are also well known. The latter condition must be differentiated from *absence of the nasal bone* and the saddle nose of congenital syphilis; all three may lead to nasal obstruction and chronic nasal discharge.

Nasal Passages

Anterior choanal stenosis and atresia are rare;[107a] the latter at least should be easily diagnosed. *Posterior choanal atresia* is inherited as a dominant trait in some families,[107] but is usually sporadic, affecting females over males in a ratio of about 2 to 1.[107a] The clinical picture of bilateral atresia is that of respiratory distress, commonly intermittent and exaggerated by feedings, in the neonatal period. The diagnosis can be made by inability to pass a nasal catheter or by instillation of radiopaque medium into the nasal passages. Whitehouse and Holt[107] described paroxysmal expiratory ballooning of the hypopharynx as a useful diagnostic sign in bilateral choanal atresia (normally the air content of the pharynx is greater on inspiration).

In about 90 per cent of cases the obstruction is bony and requires operative intervention. The transpalatine approach is generally favored, because the narrow nasal passages are easily abraded by transnasal instrumentation, and adhesions may develop which can cause as great a degree of obstruction as the original lesion.[84, 107a] Tracheotomy is often useful during operation and recovery,[6] and tube feeding may be desirable, with or instead of tracheotomy. Patients who reach later age without treatment may have, in addition to the respiratory difficulty aggravated by ingestion of liquids or solids, chronic nasal discharge and nasal voice.

Unilateral choanal atresia occurs about twice as often as bilateral atresia, and affects the right side in about two thirds of cases.[107a] Symptoms are few, mild and typically late in appearance. Transpalatine operation is again the preferred treatment.

Deviation of the nasal septum ordinarily is the result of trauma, but occasionally appears to be hereditary.[100]

Nasopharynx

Few malformations of the nasopharynx occur. *Cyst of the inner portion of the first branchial cleft* has occasionally been reported,[46] but apparently not in infancy. The differential diagnosis includes cold abscess of cervical vertebrae, choanal polyp and pharyngeal tumor. Branchial cysts occur laterally in the pharynx, in contrast to adenoid cyst and nasal encephalocele, which are situated medially. *Nasal encephalocele* (rhinoencephalocele) is rare (six cases among 546 meningoceles and myelomeningoceles in the series of Ingraham and Matson[50]). The symptoms are those of nasal obstruction, and usually appear in infancy. The sac is visible in the nose or nasopharynx as a gray, semitranslucent soft mass covered by mucosa. X-ray examination shows a defect of the skull, usually of the cribriform plate and ethmoid air cells. Aspiration or biopsy is dangerous because of the probability of meningitis, and roentgenograms of the base of the skull should be studied before any nasopharyngeal mass is attacked surgically.[5, 50] The preferred treatment of nasal encephalocele is removal by the intracranial route.

Frontal (sincipital) encephaloceles may involve the root of the nose and cause nasal obstruction, and the lesion called *nasal glioma*, which usually presents as a mass beside the bridge of the nose, probably is a pinched-off encephalocele.

A rare cause of nasopharyngeal obstruction, which has genetic implications, is *neurofibroma*.[26]

Nasal Sinuses

Hypoplasia of the nasal sinuses has been reported in a number of conditions, including mongoloid idiocy,[35] craniofacial and mandibulofacial dysostosis (see p. 75), the Kartagener syndrome (see p. 93) and Pyle's disease (familial splaying of the long bones).[17] However, variations in the development of the nasal sinuses are so common that many observations are of doubtful significance. For example, Maresh[74] states that in 5 to 10 per cent of children the frontal sinuses do not extend above the orbital roof by the age of 13 years. Similar data from others support this opinion. Thus 5 per cent of persons are said to have aplasia of both frontal sinuses and 11.5 per cent of one frontal sinus, and 30 per cent to have hypoplasia of the frontal sinuses and 6 per cent

of the maxillary sinuses. The maxillary and ethmoid sinuses are normally present at birth, the sphenoid sinus developing at about three years and the frontal sinuses at five years. Although no specific evidence is available, many variations in nasal sinus pattern are probably hereditary, and such variations may be responsible in part for familial susceptibility to sinus infection.

PALATE

A *high-arched (ogival) palate* may occur in patients with arachnodactyly and mandibulofacial dysostosis, and in several variants of the *pterygium syndrome*, most often perhaps in the *Bonnevie-Ullrich syndrome*, another variable constellation of malformations, including pterygium colli, cutis laxa and lymphangiectatic edema, ogival palate and, on occasion, malformations of the extremities, muscles (particularly pectoral and abdominal), ears, heart.[54, 57, 90] A relation of this complex to arachnodactyly and to mandibulofacial dysostosis has also been suggested.[57]

Cleft palate is, medically and economically, the most important malformation of the upper respiratory tract. The diagnosis is obvious when harelip is present, and recognition of solitary cleft palate is rarely difficult. Respiratory difficulty with feedings and regurgitation of feedings through the nose are the usual manifestations. The principles and details of the treatment of cleft palate, with or without harelip, are beyond the scope of this discussion, as is also consideration of the treatment of residual speech difficulty. In unilateral cleft palate with harelip the cleft is lateral to the midline of the palate, and in bilateral harelip and cleft palate the cleft extends across the midline. Solitary palatal cleft, on the other hand, is regularly median.

Both conditions are genetically determined (perhaps with fetal environmental factors in addition), but the two are genetically independent disorders. Solitary cleft palate affects approximately two females to one male, and cleft palate with harelip the opposite ratio. Collectively, the two conditions occur in one or two infants per 1000 births.[90, 104] Reed gives the following estimates, of value in genetic counseling:

Cleft palate alone:	
Risk for sibling of affected child, parents normal	2%
Risk for sibling of affected child, one parent affected	17%
Risk for child of affected parent	7%
Cleft palate with cleft lip:	
Risk for sibling of affected child, parents normal	4%
Risk for sibling of affected child, one parent affected	14%
Risk for child of affected parent	2%

Additional data on the genetic aspects of cleft palate are given in Sorsby.[100]

Cleft palate has been reported in association with many other anomalies, with some tendency for the solitary form to occur with other skeletal malformations, and the harelip and/or cleft palate form to occur with major malformations of the central nervous system.

The *Pierre-Robin syndrome* of micrognathia and cleft palate deserves special mention because of the severity of the respiratory distress which may be produced when the back of the tongue obstructs the pharynx. The distress may be alleviated by placing the infant face down, or tracheotomy may be needed.[6] A wire frame to hold the mandible forward and skeletal traction on the tip of the mandible may be used for definitive treatment of the micrognathia.[18, 31] The tongue may also be sutured forward to prevent it from obstructing the oropharynx.

EPIGLOTTIS AND LARYNX

Malformations of the epiglottis have probably been overemphasized as causes of respiratory distress in infancy, and there is good reason to doubt the significance of the so-called infantile epiglottis. *Bifid epiglottis* and *abnormally elongate epiglottis* can, however, cause inspiratory stridor, and elongate epiglottis may produce peculiar flapping or clucking sounds.[51, 107a]

Laryngomalacia is of uncertain etiology; it produces inspiratory stridor which is low pitched and constant. Treatment is usually not necessary, the difficulty subsiding spontaneously by the age of two to two and one-half years. A distinguishing feature of this form of "congenital obstructive laryngeal dyspnea" is the normal voice of affected infants. The diagnosis of laryngomalacia should never be made without adequate study, including direct laryngoscopy, because almost all other causes of laryngeal dyspnea in infancy require specific treatment.

Dislocation of the cricoarytenoid joint is probably the result of trauma in most cases; the symptoms include hoarseness, wheezing and cyanosis. Treatment by reduction is necessary if fatal asphyxia or permanent speech damage is to be avoided. Tracheotomy may be necessary if the respiratory distress is severe, until the laryngeal airway can be re-established. In contrast, *dislocation of the cricothyroid joint* causes a weak or hoarse voice, but rarely dyspnea, and there are usually no sequelae, even without treatment by manual reduction.[51]

Congenital laryngeal atresia is incompatible with life unless the diagnosis can be made shortly after delivery. Respiratory motion without air exchange is the clinical manifestation, and tracheotomy the treatment. A number of cases of laryngeal atresia or severe stenosis, in association with esophageal atresia and tracheo-esophageal fistula, have been reported, and this possibility should be borne in mind if respiratory

difficulty persists or recurs in a patient with laryngeal stenosis or atresia after tracheotomy.

Laryngeal stenosis produces dyspnea, cyanosis, wheezing, stridor and at times stertor, with or without hoarseness or weakness of the cry. Tracheotomy may be necessary if the signs are severe, and should be followed by laryngeal dilatation; laryngostomy may be necessary. Jackson[51] feels strongly that early treatment is desirable and that one should not wait to see whether the symptoms will be "outgrown."

Laryngeal web produces a similar clinical picture, except that there is regularly either weak cry or aphonia, and the stridor is both inspiratory and expiratory. In a review of 133 cases 75 per cent of the webs were at the level of the true cords, 1.5 per cent supraglottic, and the remainder subglottic.[48] Jackson recommends incision of one side of the web only, feeling that the results are better than with bilateral incision.

TABLE 6. *Causes of Obstructive Laryngeal Dyspnea in Infancy, Other than Anomalies of Tongue, Epiglottis and Larynx*

Laryngitis and laryngotracheitis, including croup	Foreign body of hypopharynx or larynx
Diphtheria	Retropharyngeal abscess
Tuberculosis	Goiter
Tetany	Cystic hygroma
Vocal cord paralysis	Laryngeal papilloma
	Acute epiglottitis

Thyroglossal cyst of the base of the tongue, lingual thyroid gland, laryngeal cyst and *laryngeal hemangioma* are relatively rare malformations causing laryngeal dyspnea. The two forms of cyst are treated by removal. Patients with a lingual thyroid gland often have no other thyroid tissue, and this point should be established before such a structure is removed. The proper treatment of laryngeal hemangioma is not certain.[89] Some form of cauterization or scarification, with subsequent laryngeal dilatation if necessary, is probably to be preferred to radiation and an enhanced risk of carcinoma of the thyroid in later life.

Obstructive laryngeal dyspnea is so important a pediatric problem that a list of other causes, as an aid to differential diagnosis, does not seem out of place (Table 6). In most cases a detailed history of the time of onset and the nature of the respiratory difficulty, its persistence or not, and so forth, allow differentiation of acquired from congenital disorders, but the importance of laryngoscopy and x-ray examination cannot be overstated. One must also remember than many diseases of the trachea, anomalies and otherwise, produce signs and symptoms very like those of laryngeal disease.

Laryngoceles are cystic structures, containing air, arising from and communicating with the lumen of the laryngeal ventricles.[47] They may be only intralaryngeal, and cause obstruction, or may extend through

the wall of the larynx to present as a mass in the neck, usually in the upper part of the neck, anterior to the sternocleidomastoid muscle; when large, they may extend down to the clavicle, or displace the tongue, larynx and trachea. They may be unilateral or bilateral, and may appear only on forced phonation, as crying. The symptoms include abnormality of the voice (hoarseness, weakness or aphonia), respiratory distress, cough and evidence of infection. Although in many patients laryngoceles do not appear until adult life, they occur with appreciable frequency in children, and probably all cases have a congenital basis. Large laryngoceles occur normally in certain other primates, whence the term "orang-outan neck," applied to infants whose laryngoceles became distended on crying. Surgical treatment is indicated for those sacs large enough to cause symptoms.[47]

TRACHEA AND MAJOR BRONCHI

Although, with the exception of tracheo-esophageal fistula, anomalies of the trachea and major bronchi are rare, they are important because they cause clinical confusion with similar lesions of the larynx and because treatment is relatively difficult. True *tracheal atresia*, unless so high that tracheotomy can be performed, is probably always incompatible with life. Many reports of *tracheal stenosis* actually concern the lesion discussed in the preceding section as subglottic laryngeal stenosis. However, tracheal stenosis at a lower level does occur, both as an isolated lesion and in association with tracheo-esophageal fistula.[95] In the neonatal period it requires distinction from tracheal compression by mediastinal cysts (see p. 81) and by vascular rings. The obstruction may be a web, a fibrous structure, a cartilage bar or a malformed tracheal cartilage,[45] and the treatment will differ accordingly. Wolman[108] described diffuse stenosis of the trachea caused by lack of the normal posterior membrane, so that the cartilage rings are complete. Whatever the type and level, tracheal stenosis produces a clinical picture similar to that of obstructive laryngeal dyspnea.

The term *tracheomalacia* refers to localized or more diffuse tracheal obstruction because of defect of the tracheal cartilage. It must be distinguished from tracheal compression by mediastinal masses and vascular anomalies. In all three states the patients may assume an opisthotonic position, the hyperextension of the neck stretching the trachea and widening the tracheal lumen; this sign is of considerable diagnostic value, but a similar posture is seen in some patients with congenital heart disease and cerebral vein thrombosis. Commonly, with tracheal or large bronchial compression by anomalous blood vessels, there is a cartilage deficiency at the site of compression[45] (see Fig. 30, p. 48), so that the respiratory difficulty may persist after ligation or division of

the offending vessel and require treatment by dilatation or excision of the area.

Bronchial web, stenosis or compression usually differs from corresponding tracheal lesions in having the physical findings (for example, of atelectasis or obstructive emphysema) localized to one lung or lobe, but the principles of treatment are the same as for the several types of tracheal obstruction. Bronchial compression from an enlarged heart affects the left main bronchus or its large branches, but compression by anomalous vessels may affect any main or lobar bronchi.

Anomalies of the intrapulmonary bronchi differ considerably from those under discussion, and such malformations are considered in conjunction with those of the lungs. Further, because of their general importance in the differential diagnosis of respiratory difficulty in infancy, mediastinal cysts are discussed in the next section. Tracheo-esophageal fistula is also deemed worthy of separate discussion because of its frequency (p. 83).

The terms *trachiectasis* and *tracheocele* have not been used consistently by writers in this field. Both diffuse tracheal dilatation (trachiectasis) and tracheal diverticulum (tracheocele) appear to be acquired disorders rather than congenital anomalies[4] and rarely if ever appear in childhood. Bronchogenic cysts, which have also been called tracheoceles, are discussed with other types of mediastinal cyst.

Anomalous branching of the trachea is rarely of clinical significance, except for production of confusion on endoscopy or bronchography. The most important form is separate origin of the right upper lobe bronchus above the origin of the right main bronchus.[36] The area of lung supplied may be either a part of or separate from the right lung proper, and the term *tracheal lung* has been applied to both situations. The writer has seen an infant in whom compression of an anomalous bronchus by a right aortic arch led to lobar obstructive emphysema of the right upper lobe. Anomalous branching of the trachea also occurs with some frequency in the *syndrome of situs inversus with levocardia, congenital heart disease and absence of the spleen.*[50a] The cardiac lesions are usually the cause of death; typically the heart is a cor triloculare biatriatum, with anomalous venous return (systemic or pulmonary, or both), and pulmonary atresia or absence of the pulmonary artery (pseudotruncus arteriosus).

MEDIASTINAL CYSTS

A variety of cystic malformations of the mediastinum either arise from the respiratory tract or may involve it by compression. The relative frequency of the more important types in two large series[1, 37] is given in Table 7. A brief discussion of each of the important types,

containing data useful in clinical differential diagnosis, is presented here. A much more detailed survey of mediastinal cysts is available in Schlumberger's book.[96]

The respiratory symptoms and signs which can be produced by mediastinal cysts are varied, including dyspnea, tachypnea, cough, hemoptysis, hematemesis, cyanosis, dysphagia and chest pain or discomfort. Complications of such cysts include caval obstruction, tracheal or bronchial obstruction, rupture into the pleural cavity or into the trachea or bronchi, and erosion of the esophagus or vertebrae.[20, 37] Consequent to obstruction of or rupture into respiratory passages, infection

TABLE 7. *Relative Frequency of Mediastinal Cysts*

	GROSS*	ABELL†
Gastrointestinal duplication	16	—
Cystic hygroma	5	—
Teratoma	5	—
Bronchogenic cyst	1	17
Hemangioma	1	—
Neurenteric canal cyst	1	4
Pericardial cyst	—	8
Esophageal cyst	—	3
Thymic cyst	—	2
Anterior meningocele	—	1

* 49 extrapulmonary tumors of thorax, excluding lymphoma, from children.
† 133 tumors of mediastinum, predominantly from adults.

may develop; pneumonia, lung abscess, empyema and bronchiectasis may occur. X-ray examination, both routine and special (esophagrams, bronchograms and the like), is invaluable in the clinical study of patients with mediastinal cysts. The treatment for all forms producing symptoms is surgical excision when possible.

Bronchogenic Cysts

Although presumably congenital and derived from ectopic bronchial buds in most cases, these are relatively rare in children. They may be paratracheal, carinal, hilar or paraesophageal in position; the carinal forms are most liable to produce respiratory obstruction in infancy. These cysts are lined by respiratory epithelium, and often have cartilage and tracheobronchial glands in the wall.[20, 69, 81, 96] Some, if not all, esophageal cysts lined by ciliated columnar epithelium probably should be regarded as esophageal cysts lined by embryonal esophageal ciliated epithelium rather than as bronchogenic cysts.[81]

Neurenteric Canal Cysts

These typically occur in children. They may be lined by gastric or intestinal epithelium, or both, and are connected to a vertebral defect

by a cord or canal. Vertebral anomalies (spina bifida, hemivertebrae, anomalous fusion of bodies) regularly occur, and their presence in a patient with mediastinal cyst should suggest this diagnosis.[1, 44, 96] This lesion appears predominantly in males and shows a definite association with abdominal intestinal duplication.

Gastrointestinal Duplications

These also usually cause symptoms in early life. In Gross's series 13 of 16 were considered to arise from the esophagus, but three penetrated the diaphragm to enter the small intestine. Roughly 80 per cent of duplications do not communicate with the gastrointestinal tract; when communication does occur, the cyst may contain gas. Differentiation from diaphragmatic hernia then becomes important.

Anterior Meningocele

These are rare, and their clinical significance lies in an impressive (at least 70 per cent) association with von Recklinghausen's neurofibromatosis.[23]

Pericardial (Celomic or Mesothelial) Cysts

Although considered to be malformations, these rarely if ever appear until adult life. They are situated anteriorly in the cardiophrenic angle, adjacent to the pericardium, diaphragm and anterior chest wall. They rarely cause symptoms, and are mentioned chiefly because they are easily confused pathologically with cystic hygroma.[30, 59, 69] Typically, mesothelial mediastinal cysts are unilocular.

Cystic Hygroma

This is one of the more important cystic mediastinal masses of children. It differs from pericardial cyst in being multilocular, in usually being higher in the mediastinum, and in a frequent association with the easily diagnosed cystic hygroma of the neck.[69]

Teratomas and Dermoid Cysts

Typically situated in the anterior mediastinum, these usually cause relatively little difficulty in diagnosis. They are the only cystic mediastinal lesions which show calcification with any frequency.[69]

TRACHEO-ESOPHAGEAL FISTULA

Anatomically, fistulas from the esophagus to the airway may join either the trachea or the major bronchi, but there is no clinical differ-

ence between the two situations, and they are discussed jointly in this section. With or without esophageal atresia, tracheo-esophageal fistula occurs in about one in 1000 to 2500 births (see p. 74). The clinical findings depend strikingly on the exact anatomic pattern, as outlined below, using Ladd's classification.[77]

Class 1. Esophageal Atresia Alone

The symptoms are excessive "salivation" from birth, with gagging and coughing with feedings. Intermittent cyanosis or respiratory distress may occur, and aspiration bronchopneumonia may lead to lung abscess, empyema and septicemia. X-ray studies demonstrate no air in the upper gastrointestinal tract (see Fig. 14, p. 35). Esophageal anastomosis is the treatment of choice; when it is not possible or must be delayed, gastrostomy for feeding and marsupialization or constant suction of the upper esophageal segment will prevent further aspiration and lung infection.

Class 2. Esophageal Atresia with Fistula from the Upper Segment to the Trachea

Regurgitation of saliva is less impressive, but respiratory difficulty is more marked and becomes severe with feedings. The x-ray findings and principles of surgical treatment are as for class 1.

Classes 3 and 4. Esophageal Atresia with Fistula from the Trachea (3) or the Carina (4) to the Lower Esophageal Segment

Over 80 per cent of all cases of atresia fall into these two classes. The clinical picture is the same, the anatomic difference being only of surgical significance. The basic distinction from classes 1 and 2 lies in the presence of gaseous distention of the stomach and intestine, demonstrable by physical or x-ray examination. Ligation and division of the fistula and direct esophageal anastomosis is the preferred treatment. Gastrostomy for feeding until the patient's condition permits operation is not desirable, because gastric contents can be regurgitated directly into the airway.

Class 5. Tracheo-esophageal Fistula without Esophageal Atresia

This class, although rare, is of great importance since symptoms may not become severe until later life and are often mistaken for those of asthma or recurrent lung infection.[41] Diagnostic clinical features include paroxysmal cough related to feeding, liquids usually causing more difficulty than solids; these attacks may cause cyanosis. Chronic or recurrent

pneumonitis, which may progress to bronchiectasis, habitually occurs. Gaseous abdominal distention, relieved by gastric suction, but not by rectal tube, is regularly present, and rapid inflation of the stomach with coughing can be utilized as a diagnostic sign, with the patient under fluoroscopic examination. The treatment is ligation and division of the fistula.[41, 78, 105]

In all categories of tracheo-esophageal fistula, with or without esophageal atresia, x-ray study of the esophagus and trachea is of great value. A blind upper esophageal pouch is best demonstrated by instillation of a small amount of Lipiodol or Urokon (preferred to barium because the reaction in the lungs is less marked if any of the medium is regurgitated and aspirated). The fistulous tracts themselves may be demonstrable with opaque medium instilled into either the trachea or esophagus, depending on their anatomic relations (see Fig. 15, p. 36).

The association of laryngeal or tracheal stenosis or atresia with tracheo-esophageal fistula has been mentioned. Many other congenital anomalies may be present in these patients, approximately one half of all cases showing some other anomaly. Gross[37] gives the following data on his large series:

Total cases—233

Congenital heart disease	24	Malrotation of intestine	4
Anal or rectal anomaly	23	Coarctation of aorta	4
Meckel's diverticulum	10	Vertebral anomalies	4
Atresia or stenosis of small intestine	7	Ureteral stenosis	4
		Miscellaneous	23

Congenital bronchobiliary fistula has also been reported.[82] Although this condition must be rare, it is of interest in that the coincidence of chronic pulmonary suppuration and production of green (bile-stained) sputum gives a clinical picture simulating that of fibrocystic disease of the pancreas.

Congenital bronchopleural fistula, producing tension pneumothorax in the neonatal period, has also been described.[45] This condition must be distinguished from the much more common pneumothorax in association with pulmonary interstitial and mediastinal emphysema in the immediate neonatal period, and perhaps on occasion from staphylococcal pneumonia with pulmonary necrosis or abscess leading to pneumothorax in early infancy.

LUNGS AND INTRAPULMONARY BRONCHI

The writer has not been able to devise a logically consistent outline of the many important anomalies of these structures, on either an anatomical or a clinical basis. A variety of less important malformations will therefore be surveyed, and separate sections will be devoted to the more important ones.

Variations in the pattern of the bronchi and pulmonary vessels should properly be considered variants of normal rather than anomalies. Knowledge of them is, however, of considerable significance for the correct interpretation of bronchograms and angiocardiograms, and also for lung surgery, particularly segmental resection. Analysis of the many possible variations in pattern of these structures is beyond the scope of this paper. As an aid to readers who face such problems, however, a list of references covering the anatomical, surgical and radiological aspects of bronchovascular architecture is given.[2, 9, 10, 12, 35, 52, 63, 86]

Anomalous lobation of the lungs, in the absence of other anomalies, is rarely of clinical significance, except in terms of roentogenologic localization of pulmonary lesions.[56] When the number of lobes is either increased or decreased, diseases which normally have a lobar distribution may present confusing physical signs or x-ray patterns unless the possibility of abnormal lobation is considered. Certain variations of lobar pattern, such as *azygos lobe*, medial accessory left lower lobe, lateral accessory right upper lobe and subapical (subsuperior) division of the lower lobes, are so common as to be within normal limits.[45] Azygos lobe, at least, is a hereditary trait,[24] and it is possible that the other variants are also genetically determined. Asymptomatic anomalous lobation, usually symmetrical trilobation, regularly occurs in the syndrome of situs inversus with levocardia, congenital heart disease and absence of the spleen (see p. 81).

The line between accessory lobe, accessory lung and "extralobar sequestration of the lung" is often difficult to draw, and all such malformations producing symptoms are discussed under the last-mentioned heading. Tracheal accessory lobe is another name for tracheal lung (see p. 81).

Pulmonary Agenesis

Bilateral pulmonary agenesis (congenital absence of the lungs) is rare, and of course does not permit life after delivery; it is seen in acephalic monsters.[87] *Unilateral pulmonary agenesis* often causes no symptoms if there are no major associated anomalies,[105] but the mortality rate in infancy is high because serious malformations of other organs are commonly present. Oyamada et al.[85] give a detailed survey of 73 cases of unilateral pulmonary agenesis, and list the following major anomalies associated with it:

Spine anomalies	9	Spleen anomalies	3
Ventricular septal defect	7	Atrial septal defect	3
Anal atresia	4	Diaphragmatic hernia	2
Tracheo-esophageal fistula	4	Horseshoe kidney	2
Rib anomalies	4	Cleft palate	2
Anomalous pulmonary venous return	3	Microcephaly	2
		Others	10

Unilateral agenesis of the lung occurs on the left side in about 70 per cent of cases, and affects males over females in a ratio of 2 to 1.[70] The diagnosis is usually made accidentally when the lesion is uncomplicated; the physical findings are primarily those of mediastinal shift to the affected side of the thorax. X-ray and fluoroscopic examination, bronchoscopy and angiocardiography are useful in confirming the diagnosis (see Fig. 27, p. 46). There is no treatment for pulmonary agenesis per se, but it is important to realize that treatable lesions of the upper respiratory tract may also be present.

Tracheal stenosis, bronchial stenosis in the other lung, and bronchial compression by anomalous course of the pulmonary artery have been reported in association with unilateral pulmonary agenesis.[72, 88] Development of pulmonary vascular disease with pulmonary hypertension in the residual lung has also been described.[70]

Lobar agenesis is described, but the line between this concept and that of anomalous (subnumerary) lobation is hard to draw. Again, other congenital anomalies are often present and are usually the cause of symptoms or death. An association between stenosis of the left main bronchus and agenesis of the left lower lobe has been suggested.[102]

Pulmonary Hypoplasia

Pulmonary hypoplasia may be bilateral or unilateral, and may affect the entire lung or only one or more lobes. The last circumstance leads to symptoms only if other malformations are present, but may occasionally cause difficulty in the interpretation of bronchoscopic or bronchographic findings (see Fig. 28, p. 47). The anomalies which may be associated with lobar hypoplasia are as numerous as those with pulmonary agenesis. The line between lobar hypoplasia and anomalous lobation is also difficult to define, but fortunately is of little clinical significance.

Hypoplasia of the entire lung, either unilateral or bilateral, occurs most commonly in conditions in which there is *reduction of intrathoracic space.*[77] Among these are diaphragmatic hernia, pleural effusion (usually due to fetal hydrops), intrathoracic cysts and other tumors, and cardiomegaly. Abdominal masses which produce elevation of the diaphragm also lead to pulmonary hypoplasia; these include polycystic kidneys and enteric cysts (duplications). Deformity of the spine leading to reduced thoracic volume and pulmonary hypoplasia is seen in some patients with anencephaly, and in many with achondroplasia (chondrodystrophia fetalis); pulmonary insufficiency on this basis appears to be the main cause of the high neonatal mortality of achondroplastic babies.[87] Bilateral hypoplasia of the lungs also regularly occurs in infants with renal agenesis or severe renal hypoplasia (Potter's syndrome), and presumably accounts for the fact that most

such infants die before uremia can develop; the mechanism of this lung lesion is obscure. These babies typically have an abnormal face, with micrognathia, flat nose, wide interorbital space and large, low-set ears deficient in cartilage;[87] oligohydramnios is almost always present and should cause the diagnosis of renal agenesis or other urinary tract anomaly to be suspected.

Certain other aspects of pulmonary hypoplasia, including possible associations of hypoplasia with bronchiectasis and cystic malformations, are discussed later. In unilateral absence of the pulmonary artery the lung on the affected side is often hypoplastic.

Cystic Malformations of the Lungs

Cystic malformations of the lungs may be either localized or diffuse, and either unilateral or bilateral. From a review of 381 cases Murphy[80] gives the following figures:

Solitary cyst	38%	Fluid-filled cysts	23%
Multiple cysts	62%	Air-filled cysts	77%

The cysts may be lined by bronchial epithelium or by tissue resembling alveolar lining; in the latter event differentiation from acquired emphysematous bulla may be possible only by history. Some writers feel that, in the absence of infection, fluid-filled cysts always have respiratory epithelium.[93] (See p. 90 for cystic lymphangiectasis of lung.) If the communication between a cystic lesion and the respiratory tract is freely patent, the lesion will behave as a nonexpansile cyst, whereas if the communication is functionally valved, it will behave as an expansile (balloon) cyst.[108] The pressure inside a freely communicating cyst, therefore, will be atmospheric; in a cyst with a "check-valve" opening the pressure on maximal inspiration will be atmospheric, but it may greatly exceed this value on forced expiration.[93] Since air cannot flow from a region of low pressure to one of high pressure, it is difficult to explain cysts in which the pressure will be above atmospheric in all phases of the respiratory cycle. Despite widespread belief that such cysts occur, the writer feels that the opinion is not valid and that "tension" has been given undue emphasis in thinking about expansile cystic lesions of the lungs.

Solitary (bronchial or bronchogenic) cysts appear as fluid-filled cysts if discovered early, but often become air-filled. They may occur anywhere in the lung, but perhaps most often near the hilum.[93] Some writers feel that these are allied etiologically to bronchogenic cysts of the mediastinum. An association with more diffuse pulmonary cystic disease has also been described,[40] and patients should be followed up with this possibility in mind. The differential diagnosis of solitary cyst includes tuberculosis, lung abscess, postinfectious cyst (postinfectious

pneumatocele), emphysematous bulla or blebs, intralobar sequestration (p. 90), diaphragmatic hernia, pneumothorax and lobar emphysema (p. 91).

Multicystic disease of the lungs is chosen as a term to comprise the various concepts of diffuse cystic bronchiectasis, polycystic disease and "honeycomb lung." Whether true etiologic or pathogenetic subdivisions exist within this group is not clear, but fortunately decision on this point is not necessary for this discussion. Multicystic disease of the lungs usually does not become manifest clinically until young adult life. Lichtenstein[67] reviewed 92 cases of *lobar multicystic disease*, 62 male and 30 female The right and left lungs were equally involved; in 75 cases only one lobe was affected, in 16 cases two lobes, and in one case three lobes. Of the 75 singly involved lobes, 30 were upper lobes, 18 middle lobe or lingula, and 27 lower lobes. This distribution is in contrast to that of classic (acquired) bronchiectasis. The lack of history of infection in many cases, and the regular lack of evidence of infection by x-ray examination (see Fig. 21, p. 42), support the opinion that lobar multicystic disease is due to maldevelopment. The condition has been reported in tracheal accessory lobes.[45]

More *diffuse cystic disease* also occurs. In some cases, as in the case of anencephaly and tracheal atresia described by Potter,[87] the condition is clearly congenital. Older patients typically have few symptoms, but a surprisingly high incidence of bronchogenic carcinoma has been reported in them—9 per cent of deaths compared to an estimated 1.5 per cent for the general adult population. Korol[61] states that bronchogenic carcinoma almost never occurs before the age of 30 except with "congenital cystic emphysema," and that three instances of this association have been reported in children. Whether a valid distinction exists between this condition and the form of "honeycomb lung" called "diffuse bilateral fibrocystic disease of the lungs"[49] is not certain, but the diffuse fibrosis is probably an acquired component. Although other anomalies are usually absent, the condition has been reported in patients with arachnodactyly and epiloia, suggesting that it is basically a developmental defect. Differentiation from the pulmonary involvement of fibrocystic disease of the pancreas, and the fibrocystic lung lesions of Letterer-Siwe disease, is not difficult.

The clinical findings in patients with multicystic lung disease vary, depending on the extent and severity of involvement and the presence or absence of infection. Of Lichtenstein's 92 patients, 30 had no symptoms. In 38, cough was the chief complaint; of these, 26 had purulent or foul sputum, five had fever or weakness, and three had had hemoptysis. If the lesions expand rapidly or cause obstructive emphysema of other areas of the lung, dyspnea, chest pain and cyanosis may appear.

Radiologic study is invaluable in the differential diagnosis of cystic pulmonary lesions. Campbell and Silver[19] have surveyed the basic prin-

ciples and give the following rough outline: localized cystic lesions—congenital cyst, pneumothorax, emphysematous bulla and bleb, postinfectious pneumatocele, intralobar sequestration; unilateral diffuse rarefaction—obstructive emphysema, cystic hamartoma (see adenomatous dysplasia, p. 92); bilateral diffuse rarefactions—diffuse cystic disease and honeycomb lung, diffuse obstructive emphysema.

Clinical points in favor of congenital as opposed to acquired origin of cystic lung lesions can be summarized as follows: Congenital lesions appear early in life, before apparent pulmonary infection, and usually grow in proportion to the growth of the lungs as a whole. They commonly show trabeculation, and fluid levels are rare except in the presence of infection; the adjacent lung tissue rarely shows evidence of infection. Congenital lesions rarely show spontaneous regression in size, and rupture with pneumothorax is rare, but conversion of static lesions to rapidly enlarging ones producing severe symptoms suggests congenital malformation.

The principles of treatment of cystic malformations of the lung are simple. It is permissible to watch lesions producing no symptoms, and apparently not infected, bearing in mind that they may enlarge rapidly. Antibiotic treatment and postural drainage are used for complicating infection, and surgical removal should be done whenever possible for infected lesions or those producing symptoms because of size. Preoperative and postoperative routines for such patients are given by Swan and Aragon.[103] Extirpation of the cyst should be performed with maximal conservation of normal pulmonary tissue because of the possibility of appearance of new lesions. Cases with more diffuse involvement cannot be treated surgically, but must be handled with antibiotics and drainage. Prophylactic administration of antibiotics to patients who have no symptoms or have diffuse disease should be considered, and all patients on whom operation is deferred for any reason should be followed up closely if respiratory tract infections develop.

Diffuse cystic lymphangiectasis of the lungs was in the past usually confused with cystic malformation of the lung tissue proper.[64] It usually causes symptoms in the neonatal period, and has been reported with arachnodactyly and congenital heart disease. There is no treatment.

Intralobar sequestration is a form of cystic anomaly deserving special mention.[11, 16, 58, 73, 109] The name implies that the affected area does not communicate with the respiratory tract, but is misleading since a high proportion of lesions contain air or air plus fluid.[58] Pathologically, the process consists in an area of cystic malformation, typically in a lower lobe and perhaps more commonly on the right. The distinguishing feature is that the arterial supply to the sequestrated area is systemic, usually by a single large vessel from the aorta or one of its main branches. Infection is common, and the clinical picture is that of chronic and recurrent suppurative disease, with cough, chest pain, chills,

fever, weight loss and hemoptysis. Roentgenograms show localized cystic disease, often with air-fluid levels (see Fig. 23, p. 43), and the diagnosis of lung abscess, bronchiectasis or tuberculosis is commonly made. Perforation, with empyema or pneumothorax, may occur, and superimposed tuberculous infection has been reported.

Treatment consists in surgical removal of the affected lobe. The presence of the large systemic artery must be recalled, because severe and even fatal hemorrhage has followed its accidental severance;[11, 73, 109] occasionally the artery can be seen in preoperative roentgenograms. Typically, there is no pulmonary artery supply to the affected area, and angiocardiography can be used to demonstrate this. Bronchograms usually show poor filling of the lesion, but absence of all connection with the respiratory tree appears to be rare.

Although probably more allied to the anomalies of tracheobronchial branching and pulmonary lobation, *extralobar sequestration* of the lung is discussed at this point because of the similarity in name to intralobar sequestration and because the two conditions have occurred together. Extralobar sequestration denotes the occurrence of lung tissue which does not communicate with the respiratory tract, either attached to the lung or separate from it. The mass is usually cystic and is supplied by systemic arteries. In contrast to intralobar sequestration, this condition occurs overwhelmingly (about 90 per cent) on the left side[27] and is often associated with diaphragmatic hernia. Infection is rare, and x-ray examination shows a water-density mass in the region of the left lower lobe in most cases. The sequestered mass may be attached to the lung, within the diaphragm or below the diaphragm. Fistulas to the esophagus and to the stomach have been reported,[34] but are rare. Similar lesions, but connected to the respiratory tract, have been called accessory lung[25] (see also tracheal accessory lobe, p. 86).

Lobar Obstructive Emphysema

Lobar obstructive emphysema is distinguished from lobar cystic disease by the appearance of severe respiratory distress, with wheezing, dyspnea, cyanosis and retractions, shortly after birth.[7, 60] Physical examination shows hyperresonance, but diminished breath sounds, over the affected area, and evidence of atelectasis of other lung regions. Roentgenograms show striking expansion and radiolucency of the involved lobe, with shift of the mediastinum to the opposite side, herniation of the emphysematous area through the anterior mediastinum, and atelectasis of the remaining pulmonary tissue. The mediastinal herniation is best shown on lateral roentgenograms (see Fig. 20, p. 41), which demonstrate the air-filled tissue in front of the heart or upper mediastinal structures. Differential diagnosis includes lobar cystic disease, pneumothorax, pneumomediastinum, and atelectasis with compensatory

emphysema. The majority of successfully handled cases in the literature were treated by lobectomy, usually with gratifyingly prompt relief of symptoms. Korngold and Baker proposed that treatment by aspiration be used[60] and described good results, but the risk of recurrence would seem to be great.

In roughly half of the reported cases bronchial obstruction by mucosal folds, cartilage defects or pressure by anomalous vessels has been described,[7, 42, 60, 93] and undoubtedly in many surgically treated cases the line of excision was distal to the obstruction. Some writers feel that the condition is due to diffuse malformation of the involved lobe, and the term "congenital hypertrophic emphysema" has been applied. Others have proposed that diffuse pulmonary fibrosis, on a developmental basis, leads to inelasticity of the lungs and subsequent emphysema.[7] The writer feels that both concepts are in error, for the aerodynamic reason given above, that air will not move from a region of low to one of higher pressure; bronchial obstruction leading to obstructive emphysema is the only apparent explanation for the usual behavior of lobar emphysema. The occurrence of a similar process in several smaller areas of the lung has been reported,[42] and no doubt postinfectious pneumatocele is often on such a basis.

Adenomatous Dysplasia of the Lung

This term is proposed for a condition which clinically may simulate lobar obstructive emphysema (more properly, which is one cause of lobar obstructive emphysema) and has been described as "congenital adenomatoid malformation" of the lung. In a review of 10 cases Ch'in and Tang[22] found one lobe to be involved eight times, two lobes twice, a whole lung once and both lungs once; of the lobar lesions, five were on the left and three on the right. Grossly, the involved area is large and multicystic. Microscopically, the tissue shows many thin-walled, irregular spaces lined by "bronchiolar" epithelium. The spaces are larger than normal alveoli and antra, and no cartilage is present between them. A high proportion of affected infants have anasarca, perhaps due to pressure on the great veins or heart, and many are born dead. Liveborn infants may show rapidly progressive distention of the affected areas, presumably because of check-valve trapping of air by the irregular thin-walled spaces, and both clinically and roentgenographically may have the picture described in the preceding section. The writer recently saw a case of involvement of the left lower lobe and lingula leading to striking overdistention, mediastinal shift and herniation, and atelectasis of the right lung. The infant died despite resection of the left lower lobe. Microscopic sections showed the changes just described, with many striated muscle fibers in the septa. Similar, if not identical, lesions have been described as hamartoma of the lungs and as pulmonary anlage

tumor,[39] but neither concept seems truly applicable. Undoubtedly, many reports of congenital bronchiectasis really refer to this condition.

Congenital Alveolar Dysplasia

This concept is mentioned only because it occurs in the literature. By congenital alveolar dysplasia is meant relative immaturity of the lung to an extent incompatible with life.[71] Although relative immaturity of hypoplastic lungs with diaphragmatic hernia does occur, the writer has never observed such a lesion as a diffuse and isolated malformation. In his opinion, use of this concept to explain many neonatal deaths is in error, and the original descriptions appear to represent misinterpretation of the neonatal hyaline membrane condition. For the same reason he believes that theories attributing other lung lesions to late effects of congenital alveolar dysplasia[7] are also in error.

Kartagener's Syndrome

In true form this is a familial condition characterized by bronchiectasis, situs inversus of the viscera and chronic nasal sinusitis (Kartagener's triad). The symptoms of respiratory difficulty and infection usually appear in infancy, but there is little if any evidence that the bronchiectasis is already present. In other words, the bronchiectasis is probably the usual postinfectious bronchiectasis, and the mechanism of the original susceptibility to infection is not known. In families with the condition some members may have the full triad, some only bronchiectasis or sinusitis, and some only dextrocardia with or without the respiratory tract involvement.[28, 110] This suggests that simple mechanical relations are not responsible for the association of all three components of the triad. In partial form this syndrome is probably relatively common, since bronchiectasis appears to be more frequent in persons with situs inversus or dextrocardia than in the general population (estimated 22 per cent in situs inversus, 14 per cent with dextrocardia, 0.5 per cent at random).[28, 110] Congenital heart disease is common with dextrocardia, and appears to be more frequent than random in patients with Kartagener's syndrome, as well as the cause of death in some. If the condition is inherited as situs inversus, the trait is probably a simple recessive.[110]

Hamartoma of the Lung

Masses of mesenchymal tissue variously including fat, muscle, connective tissue, cartilage and blood vessels, with or without abnormal bronchiole-like respiratory channels, have been called hamartomas of the lung,[55] pulmonary anlage tumors,[39] hemangiorhabdomyoma of the lung[87] and other terms.

The masses are present at birth and may be so large as to cause death

in the neonatal period. The age incidence suggests that the lesions are malformations of some sort, and perhaps in the broad sense hamartomas, but this term was pre-empted long since for another condition, chondromatous pulmonary hamartoma. This condition is common, occurring in perhaps one in 400 persons,[68] and apparently does not occur before the age of 21. Typically, these hamartomas are small, slowly growing nodules located in the periphery of the lung and composed of lobules of mature cartilage separated by connective tissue and occasionally small air passages. Males are affected over females in a ratio of 2 or 3 to 1.[65, 92] By x-ray examination they are sharply circumscribed and round or lobulated; many show focal calcification. The differential diagnosis includes bronchogenic carcinoma, tuberculoma, chronic lung abscess, fluid-filled cyst, infarct, arteriovenous fistula of the lung, and metastatic tumor. The majority cause no symptoms, but a few produce cough, chest pain or dyspnea on exertion.[65, 101] A small proportion (10 to 15 per cent) are endobronchial and produce obstruction leading to recurrent pneumonitis, purulent sputum or hemoptysis.[98] Bronchoscopic resection can be performed for these. Malignancy has not been reported in chondromatous pulmonary hamartoma.

Pulmonary Arteriovenous Fistula

Although this condition does not commonly produce symptoms in children, it is of interest to pediatricians in that it is one manifestation of familial hemorrhagic telangiectasia (Osler's or Rendu-Osler's disease). Fifty to 60 per cent of patients with pulmonary arteriovenous fistula have either hemorrhagic telangiectasia or a family history of it, and perhaps 25 per cent of persons with hemorrhagic telangiectasia have pulmonary arteriovenous fistula. Genetically, the trait is a dominant with relatively high penetrance and no sex distinction; there is some evidence that the homozygous form is lethal in early life.[90] The lesions appear roentgenographically as lobulated or round shadows with discrete margins; they are commonly multiple, the apices being the areas least often involved.[68] Occasionally the afferent and efferent vessels running to and from the hilum are visible. A diagnostic sign of some value is decrease in size of the lesions during the Valsalva maneuver (forced expiratory motion with the glottis closed) and increase in size with the Müller maneuver (forced inspiratory motion with the glottis closed).[76, 97] Affected patients often show cyanosis, digital clubbing and polycythemia, and a bruit can be heard over the lesion. The peripheral pulse pressure is normal, and evidence of cor pulmonale is rare. The treatment consists in surgical excision of the lesions, but it is important that as little lung tissue as possible be removed, since new lesions may develop in other areas of the lung.[21]

Whether the rare, large cirsoid arteriovenous aneurysms of the lung,

with involvement of the adjacent thoracic wall, have the same genetic background as the smaller lesions just described is not certain.[62] The treatment of these is also surgical, but is hazardous because of the difficulty of controlling bleeding while the involved lung is separated from the chest wall.

ANOMALIES OF THE DIAPHRAGM

Diaphragmatic hernia is the clinically most important anomaly of the diaphragm. These hernias occur in three different sites—the esophageal hiatus, the retrosternal foramina of Morgagni and the posterolateral foramina of Bochdalek. When the herniation occurs through the esophageal hiatus or the foramina of Morgagni, the viscera which protrude into the thorax are covered by a serosal sac, but a sac is present in only about 10 per cent of posterolateral hernias. When a sac is present in the latter site, the condition is spoken of as *eventration of the diaphragm* (see Fig. 26, p. 46). Gross[37] gives the following data on relative frequency of hernia in these various sites:

Left foramen of Bochdalek	69 cases
Right foramen of Bochdalek	13 cases
Esophageal hiatus	5 cases
Foramina of Morgagni (either or both)	4 cases

Hernias in the latter two sites are typically small and cause only minor symptoms. However, the posterolateral hernias are usually large, with much of the abdominal content displaced into the thorax, and a high proportion of such patients die in the neonatal period. The symptoms commonly include cyanosis, dyspnea and other features of respiratory distress; these may be relieved if the patient is placed with the affected side down. Occasionally respiratory difficulty when the infant lies on one side (usually the right) is the first clue to the presence of such a hernia. Physical findings include decreased respiratory excursion and breath sounds on the affected side, a scaphoid abdomen with decreased tympany, peristaltic sounds in the involved hemithorax, and a variable percussion note. The x-ray findings are usually diagnostic (see Figs. 24, 25, pp. 44, 45), but occasionally there may be confusion with multicystic disease of the lung, lobar obstructive emphysema, pneumothorax or intrathoracic tumor.

Surgical repair of the hernia is the treatment of choice. The abdominal cavity is commonly small, and at times replacement of the herniated viscera may be difficult or may lead to such a degree of diaphragmatic elevation that adequate respiration is not possible. The lung on the side of the hernia is typically hypoplastic, and vigorous attempts to expand it after repair of the hernia are not justified. The writer has seen a number of such infants die of pneumothorax or mediastinal emphysema due to rupture of the hypoplastic lung by excessive positive pressure.

There is reason to believe that the lung will grow to relatively normal size if left alone, and it is often so small as to be of little or no aid to the infant if the other lung cannot support life in the postoperative period.

Partial *duplication of the diaphragm* (accessory diaphragm) has been reported at least twice.[29, 94] In both patients the right middle lobe was hypoplastic, and the right lower lobe in one and a portion of it in the other were below the accessory diaphragmatic leaf; one patient also had anomalous venous drainage of the right lower lobe to the inferior vena cava.

ANOMALIES OF THE THORACIC CAGE

Many clinically insignificant anomalies of the ribs, sternum and muscles of the thoracic wall occur, but the only ones discussed here are *pectus excavatum* (funnel chest, chonechondrosternon) and related deformities. Opinion has grown in recent years that the basic lesion in this condition is abnormal development of the diaphragmatic tendons.[14, 15, 66] If the central tendon of the diaphragm is abnormally short, the xiphoid and lower sternum are retracted. When the lateral tendons are short, a transverse groove resembling Harrison's groove of rickets is present on both sides of the chest. If only one lateral tendon is abnormal, the groove is present on only one side, and the sternum is slanted toward the affected side. If both the central and lateral tendons are involved, both funnel chest and bilateral groove are present. The condition is said to be present from birth,[15] but is often missed until later childhood. In infants separation of the xiphoid from the gladiolus of the sternum has been used to relieve the pull on the latter, but the procedure is not too effective,[66] and a more elaborate surgical procedure is necessary for severe cases.[66]

The occurrence of pectus excavatum as a familial trait, both alone and in association with arachnodactyly and von Recklinghausen's neurofibromatosis, has been described.[53, 90] Whether the respiratory symptoms which may occur in patients with pectus excavatum are due to pulmonary compression or to deviation and compression of the heart and great vessels is not certain.

ASSOCIATION OF OTHER ANOMALIES WITH THOSE OF THE RESPIRATORY TRACT

Complete care of a patient with an anomaly of the respiratory tract requires not only diagnosis and treatment of that lesion, but also recognition of the fact that malformations of other organs are commonly present. Whenever possible in the preceding pages, such associations which appear to have more than random frequency have been pointed out. However, the vagaries of the "multiple anomaly syndrome" are so great that many important associations have undoubtedly not been mentioned. It behooves the physician to have a high index of suspicion,

and not to assume too easily that all symptoms in a patient are due to the most obvious malformation.

GENETIC IMPLICATIONS OF RESPIRATORY TRACT ANOMALIES

Impressive evidence has accumulated in recent years to indicate that many, if not all, so-called sporadic congenital anomalies are basically genetically determined. In other words, in a family of given genetic

TABLE 8. *Examples of Genetic Aspects of Respiratory Tract Malformations*

CONDITION	RESPIRATORY TRACT MANIFESTATION	MODE OF INHERITANCE
Anencephaly	Rhinodymia (nasal duplication) Hypoplasia of lungs	?
Arachnodactyly (Marfan's syndrome)	Pectus excavatum Cystic lymphangiectasis Anomalous lobation of lungs Bronchial stenosis	Usually dominant with incomplete penetrance
	Cleft palate (alone)	?
	Cleft palate (with harelip)	? Simple recessive with about 20% penetrance ? Genetic plus environmental factor
	Choanal atresia	Sometimes dominant
Craniofacial dysostosis (Crouzon's disease)	Maxillary sinus hypoplasia	Irregular dominant; ? about 50% of cases sporadic
Epiloia (Bourneville's disease, tuberous sclerosis)	Miliary radiodensities in lung[99] "Fibrocystic disease"	Irregular dominant with variable expressivity
Familial hemorrhagic telangiectasia (Osler-Rendu-Weber)	Pulmonary arteriovenous fistula	Dominant with reduced penetrance
Kartagener syndrome	Sinusitis, bronchiectasis	?
	Laryngeal papillomatosis	?
	Laryngeal stenosis	?
Mandibulofacial dysostosis (Treacher Collins or Franceschetti syndrome)	Maxillary sinus hypoplasia Micrognathia Middle ear malformations	Irregular dominant
Neurofibromatosis (von Recklinghausen)	Pectus excavatum Pharyngeal neurofibroma Anterior meningocele	Dominant with high penetrance
	Pectus excavatum (alone)	Occasionally dominant; usually sporadic
Pierre-Robin syndrome	Micrognathia Cleft palate	?
Hypo (a-) gammaglobulinemia	Probably recessive; ? sex linked in some pedigrees	
Fibrocystic disease of pancreas	Probably simple recessive	
Familial dysautonomia	? Simple recessive	
Gargoylism	Usually recessive, with (?) partial manifestation in heterozygotes	
Mongoloid idiocy	Genetic plus environmental factor(s)	

composition a variety of "environmental" nocia can act to produce similar results. This tendency of similar or identical anomalies to be present even in distant relatives is well shown in Murphy's data;[79] in his material, in 41 per cent of cases in which a distant relative had a congenital defect, it was of the same type as that in the propositus. Parents of malformed children deserve to be informed, therefore, that there is a greater than random chance that subsequent children will be malformed and that the malformation will be of the same type. Cheerful reassurance that lightning does not strike twice is neither justified nor safe.

For certain types of malformations the role of heredity is even more clear-cut. Many of these have already been discussed, but for convenience the more common hereditary conditions affecting the respiratory tract, both directly and indirectly, are listed in Table 8. For such diseases, parents of an affected child deserve to know not only the risk for future children, but also the risk for offspring of the affected child and for those of his clinically normal siblings. The importance of this matter in "preventive pediatrics" cannot be overstressed. For more detailed presentation of data, the reader is referred to Sorsby[100] or to similar manuals of human genetics, and for advice on genetic counseling to the excellent little book by Reed.[90]

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UNIDENTIFIED NONBACTERIAL INFECTIONS OF THE NASOPHARYNX

The Common Cold

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The most common illness of man that involves the nasopharynx is acute nasopharyngitis of unknown etiology, or the common cold. Although not a serious disease, it contributes greatly to the misery of mankind, is responsible for the loss of many man-hours of working time and is particularly troublesome to the pediatrician.

Certain specific infections such as pertussis, diphtheria, scarlet fever, Q fever, influenza, lymphocytic choriomeningitis or psittacosis may mimic the common cold at some stage in their development. Noninfectious agents or nervous stimuli may produce the same symptom-complex. These include chemical irritants, allergens and vasomotor responses. It is not always simple to differentiate the symptoms resulting from such noninfectious causes from the true infectious cold.

The usual prodromal symptoms of a cold are irritation and dryness of the nasal passages and nasopharynx followed by a chilly sensation, vague muscular aching, itching of the eyes, sneezing and a profuse, watery nasal discharge. Headache, anorexia, irritability, hoarseness, and impairment of hearing and smell may all contribute to the patient's discomfort. The disease usually lasts about one week, although a purulent nasal discharge may persist for two weeks or longer. The infant of six months or less often has coryza without other symptoms. The accompanying nasal obstruction may interfere with feeding and sleeping. The older child somewhat more frequently manifests fever. Although

as a rule easily recognized, the common cold will show considerable variation in severity and symptomatology from season to season and from person to person.

ETIOLOGY

The common cold is now generally considered to be an infectious disease due to a virus or viruses. The evidence for the viral etiology is almost limited to the demonstration that bacteria-free filtrates of the nasal secretions of persons exhibiting the symptoms of the common cold will induce a similar illness when introduced intranasally into human volunteers. Such observations have been repeated by many investigators since the early experiments of Kruse[19] and Foster[15] in 1914 and 1917, respectively. However, these experiments are not easy to perform and are often difficult to interpret. This is particularly true since no more than 50 per cent of volunteers have symptoms after inoculation with infective material, and frequently the rate is even lower. The elaborate precautions that must be observed and the difficulties experienced in studies with human volunteers are well described by Andrewes[1, 2, 4, 21] in his discussion of the Common Cold Research Unit in the Harvard Hospital, Salisbury, England.

No suitable method has been found to propagate in the laboratory the etiological agent of the common cold. The only animal that appears to be susceptible is the chimpanzee.[10, 11] However, because of their expense and the problems of caring for them, these animals have not been used to any great extent.

Both the chick embryo and tissue culture have been extensively investigated as media for the growth of the common cold virus. Some successes have been reported for both methods. However, in most instances the results have not been confirmed. The most recent report concerning propagation of this agent is that of Andrewes.[3] He reported cultivation of this agent in tissue cultures of human embryonic lung. The filtrate used as original inoculum for the tissue cultures produced illness in half of a group of human volunteers. Material derived from tissue cultures representing the tenth passage in culture produced symptoms in only 10 per cent of volunteers. This suggests that the virus may have lost virulence for man during the course of passage in culture. No means, other than inoculation of human volunteers, has been found to indicate the presence of virus in the cultures. Thus, as yet, this observation has limited practical value.

Both Dochez[10] and Smillie[23] conducted careful and extensive studies of the changes in bacterial flora of the nasopharynx accompanying respiratory infections. Neither study revealed any evidence that bacteria initiated the symptoms of the common cold. However, certain organisms considered to be pathogenic, such as the pneumococcus and *Hemophilus influenzae*, tended to appear in greater numbers as the illness progressed. Thus bacterial infection may contribute to the persistence of symptoms in an illness caused by a viral agent.

EPIDEMIOLOGY

The information available concerning the incidence of the common cold, its mode of transmission under natural conditions, the influence of certain environmental factors and immunity is largely the result of epidemiological observation and the studies with human volunteers conducted by the Common Cold Research Unit in England[1, 2, 4, 21] and by the Commission on Acute Respiratory Diseases[8] in this country.

INCIDENCE

The number of respiratory infections suffered per person has been reported as one to six per year.[5, 6, 26] This variation is probably dependent upon the number of children in the study, upon the definition of a respiratory infection and the care with which illnesses were recorded. In a study of a selected group of Cleveland families now in its tenth year,[5] Dingle and his associates found that on the average each person had 10 illnesses per year. Six of these were respiratory illnesses!

Host Factors

The studies of Buck,[6] Downes[26] and Badger et al.[5] all show that the incidence of respiratory infections varies with age. Figure 31 shows that children less than one year of age had on the average seven illnesses per year. Between one and six the rate remained fairly constant at eight per year, but thereafter it fell progressively with increasing age. The adult rate averaged 4.8 illnesses per year. Downes'[26] figures are lower, but they too show the highest attack rate during the early years of life, a slight peak during adolescence and then a low, fairly constant rate during adult life.

The relative resistance to the common cold of the older person as compared to the child would naturally be assumed to be due to immunity resulting from previous infections. However, there is evidence that specific immunity does not develop after the common cold. If these observations prove to be correct, the resistance associated with age must be due to some mechanism other than specific immunity. Direct evidence for such a nonspecific type of resistance to another respiratory virus has been obtained by observation[16] of the secondary attack rates in persons tested and found to be without specific antibody at the time of exposure to adenovirus within the family. It was found that 55 per cent of the children exposed became infected, whereas only 10 per cent of susceptible adults were affected.

Environmental Factors

The frequency of contact outside the home would seem to influence the incidence of respiratory infections. Preschool children with no sib-

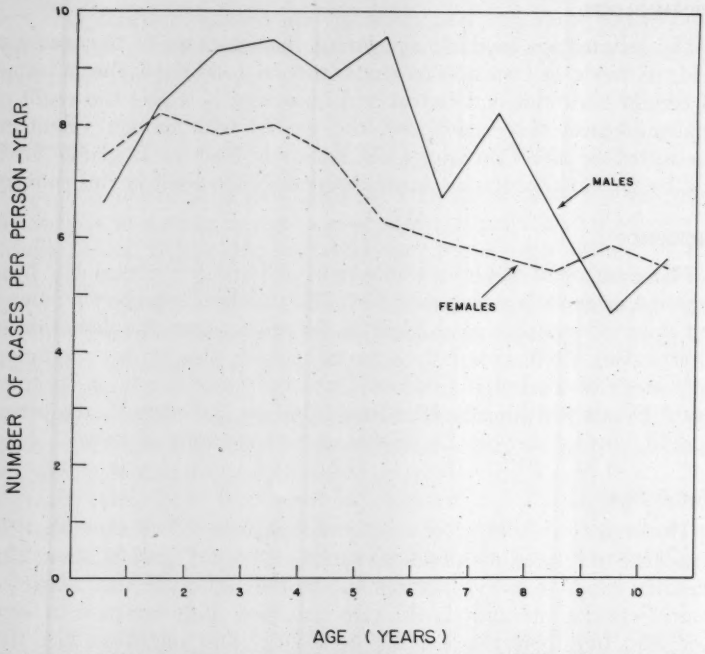

Fig. 31. Incidence of common respiratory disease among children by age and sex, 1948–50. (From G. F. Badger, J. H. Dingle, A. E. Feller, R. G. Hodges, W. S. Jordan, Jr., and C. H. Rammelkamp, Jr.: A Study of Illnesses in a Group of Cleveland Families. II. Incidence of the Common Respiratory Diseases. *Am. J. Hyg.*, Vol. 58. Reprinted by permission of the publishers.)

lings in school were found to have the fewest illnesses.[5] Children of the same age in school or with siblings in school had much higher rates of infection. As might be expected, the school age child was most often found to be the source of infection for other members of the family.

The common cold is most frequent between September and April, corresponding to the time when school is in session and indoor crowding is greatest.

It is a popular belief that exposure to low temperatures increases the incidence of colds. A number of observations suggest that this may be the case. Shade[25] reported a fourfold increase in the incidence of respiratory infections among 17,000 German troops when the weather became severe. Paul[24] noted that epidemics of the common cold occurred aboard the icebreaker *Carnegie* upon entering cold ocean currents, although the vessel was weeks out of port.

Various hypotheses have been advanced to explain the presumed

effect of environmental temperature upon development of symptoms of the common cold. It has been variously proposed that exposure reduces the person's general resistance, that it may render the mucous membranes of the nasopharynx unduly susceptible to infection through resulting vasomotor reflexes or by other means, or that exposure in some way activates a latent infection.

The observations of Milam and Smillie afford evidence against the hypothesis that activation of latent infection is an important phenomenon. On the island of St. John[23] the incidence of colds increased shortly after a drop in air temperature. On analysis it was found that illness did not occur simultaneously in a large group of the population, as would be expected if activation of latent infections had occurred. Rather, the disease spread in waves from a central focus with a constant interval between the peaks in disease incidence.

Probably the most significant information concerning the relationship of environmental temperature and the common cold is provided by direct experimentation with human volunteers. Chilling and exposure did not affect the susceptibility of human volunteers to experimentally induced colds, nor did these measures have any provocative effect.[4]

The epidemiological evidence that the common cold is passed from person to person in the course of normal social contacts is convincing. How intimate the contact must be, the role of droplet infection and the importance of indirect contact are matters that the English workers[21] have attempted to investigate in human volunteers. They found that infections occurred in volunteers after normal social intercourse, such as playing cards, for a limited time with a person suffering from a cold, or as a result of contamination of the air with a mist of infective nasal secretions. However, the rate of infection under such conditions was much lower than when the infectious material was dropped into the nose.

Indirect contact such as entering a room previously occupied by an infected person or even placing infective material on the external surface of the nose did not result in infection of the volunteers. Experiments with contaminated handkerchiefs and gauze packs introduced into the nares suggested that the infectious agent was rapidly inactivated by drying.

Thus it would appear that, in order to transmit the common cold, contact must be rather intimate and that the infectious material must gain access to the mucous membranes of the nasopharynx without opportunity for drying. Indirect contacts would appear to be of little importance.

Although the person with overt symptoms of the common cold is

usually responsible for spreading that disease, it is also likely that well persons may carry the etiological agent and spread illness while they themselves remain free of symptoms. Studies of isolated communities[24] have shown that the arrival of healthy visitors may be followed by epidemics of respiratory infections among the natives.

The duration of the carrier state can be estimated from observations made in days of less rapid transportation. Woolley, quoted by Andrewes,[4] noted that in Tristan da Cunha, epidemics of colds followed the arrival of ships from Capetown, 12 days distant by sea. No epidemics followed the arrival of ships coming from Panama around Cape Horn, a journey lasting weeks. This observation suggests that the cold virus does not persist in a small isolated population longer than a few weeks.

The little information available concerning the time during which a person with the common cold is infectious has been obtained from volunteers with the experimentally induced disease. In these subjects[4] the virus was found in the nasal secretions 24 to 36 hours before the appearance of symptoms, and persisted for as long as seven days.

Immunity to the common cold, if it exists at all, is apparently of brief duration. In the chimpanzee Dochez[11] noted an interval of decreased susceptibilty one to three months after recovery from an acute infection. In Spitzbergen,[24] an isolated Arctic community, 75 per cent of the winter residents had respiratory infection within 30 days after resumption of steamer traffic in the spring, and 90 per cent experienced at least one cold by the end of the shipping season. Similar epidemics recurred yearly. It was also noted that numerous natives suffered from multiple colds during a particular season; the illnesses occurred at intervals of 23 days to seven weeks. These observations indicate that no protection persisted from one year to the next and that in many persons the period of immunity, if any, was much shorter.

Observations on the occurrence of the common cold in families and among school children are in accord with those made in Spitzbergen. These studies also show that persons who have had many respiratory infections during a particular season are as likely to become ill during the next year as are those without such a history of previous infection.

It might be suspected that failure to acquire immunity to the common cold is due to the fact that it is caused by a multitude of antigenically different agents. The experiments conducted by the Commission for Acute Respiratory Diseases[8] would suggest that this is not so. Human volunteers were inoculated with infective filtrates from a patient with what they termed the "severe common cold." The illness was successfully transmitted. Nineteen days later the subjects were found to be equally susceptible on reinoculation with the same material.

TREATMENT

No specific therapeutic measure against the causative agent of the common cold is available. Since bacteria have not been shown to produce the common cold, no benefit could be expected from the antimicrobial agents in the treatment of the acute illness. Indeed, those studies that were conducted with proper controls have confirmed this impression.[14] The antimicrobials are useful only for the treatment of the complications due to bacterial infection.

All that the physician can offer is reassurance and therapy designed to alleviate the patient's symptoms. Acetylsalicylic acid is probably the most useful of all drugs for the relief of the systemic complaints. Parents of young infants should be instructed carefully as to the possible dangers of salicylate poisoning from excessive dosage. Nose drops not only afford temporary relief from nasal congestion, but also in children may have some value in decreasing the likelihood of infection of the middle ear.

In small infants nasal obstruction may interfere with feeding, and nose drops should be administered shortly before feeding time. Increased humidity is sometimes desirable, again particularly for infants. In general, the antihistaminic drugs have proved disappointing[13] and are not usually recommended for children. Finally, increased rest is usually prescribed. However, it is probably not of sufficient value that it should be insisted upon if the child does not feel ill and, as is often the case, vigorously resists efforts to restrict his activities.

COMPLICATIONS

Complications of the common cold are more frequent in infants and young children than in adults. When the clinical course and physical examination indicate the development of a complication such as otitis media, which is the most common, pneumonia or sinusitis, proper treatment should be instituted. The persistent purulent nasal discharge sometimes seen following colds in young children may be pneumococcal* in etiology and responds well to antibiotic therapy. The routine use of antimicrobial agents to prevent bacterial complications in the common cold is not recommended. Evidence concerning other acute illnesses would indicate that prophylactic antibiotic therapy does not necessarily prevent complications, but rather modifies the type of organism causing the infection. Needless to say, in such instance the infecting organism is invariably resistant to the agent used for prophylaxis. An additional reason for avoiding the indiscriminate use of anti-

* E. A. Mortimer, Jr.: Unpublished data.

biotics is the possibility of unnecessarily sensitizing children to these drugs.

PROPHYLAXIS

Viral Vaccines

Since the causative agent or agents of the common cold have not been isolated, no specific vaccines are available. The poor immunity that seems to result after an infection would suggest that even if a specific vaccine could be prepared, it might have little or no effect. The vaccines prepared from the adenoviruses that are presently being tested in military groups can be expected to have little value for children or civilians in general, because these agents have been found to be responsible for less than 1 per cent of the respiratory infections[16] in the general population and also have not been related to the common cold per se. Likewise, although influenza virus vaccines are moderately effective as specific immunizing agents, they do not influence the incidence of common respiratory diseases.

Bacterial Vaccines

Vaccines prepared from various bacteria isolated from the respiratory tract have been proposed as prophylactic agents for common respiratory disease, and have been referred to as "cold vaccines." However, in controlled studies they have not been found to be beneficial.[9, 17]

Atmosphere Control

Ultraviolet light,[12] glycol vapors, air filtration,[20] oiled bedding[7] and floors all have been used in an attempt to decrease the incidence of respiratory infections. These measures decrease the number of bacteria in the atmosphere, but do not prevent epidemics; nor do they significantly reduce the over-all incidence of upper respiratory tract infections.[7, 12] Such observations are in conformity with the evidence indicating that transmission is chiefly accomplished by intimate contact.

Tonsillectomy

The relationship of the tonsils to the frequency of respiratory infections has been the topic of many reports and is firmly established in our folklore. This problem has been studied in many ways, and the results are diverse. To obtain reliable information one must have the opportunity to study a group of children before and after tonsillectomy and also to compare them with children of the same age. McCorkle[22] observed the occurrence of respiratory disease among all children in the Cleveland family study population three years and older and compared

those with tonsils and those with tonsils removed. The rates in the two groups showed no significant difference. The occurrence of respiratory infections before and after tonsillectomy in a group of 26 children was also compared. These children (Table 9) were between five and nine years of age at the time of tonsillectomy. The attack rate of common respiratory infections during the year before tonsillectomy was 27.3; the rate for the year after was 18.2, but when these rates were corrected for age and season, based on the experience of children of the same age

TABLE 9. *Observed and Expected Attack Rates of Common Respiratory Disease According to Time before and after Tonsillectomy**

YEARS BEFORE OR AFTER TONSILLECTOMY	PERSON-DAYS	NUMBER OF CASES EXPECTED	NUMBER OF CASES OBSERVED	RATES PER 1000 PERSON-DAYS	
				Expected†	Observed
Before operation:					
Third year or earlier	2725	55	65	20.2	23.9
Second year	4546	104	114	22.9	25.1
First year	7716	166	180	21.5	23.3
Year of tonsillectomy	5310	119	145	22.4	27.3
After operation:					
Year of tonsillectomy	4063	66	74	16.2	18.2
First year	7886	163	166	20.7	21.0
Second year	5607	105	126	18.7	22.5
Third year or later	3383	63	58	18.6	17.1

† Expected numbers based on age- and season-specific rates for entire population.

* From L. P. McCorkle, R. G. Hodges, G. F. Badger, J. H. Dingle and W. S. Jordan, Jr.: A Study of Illness in a Group of Cleveland Families. VIII. Relation of Tonsillectomy to Incidence of Common Respiratory Diseases in Children. *New England J. Med.*, Vol. 252. Reprinted by permission of the publishers.

who had not had their tonsils removed, it became apparent that the operation did not materially alter the average incidence of common respiratory disease.

Other

Antihistamines, gamma globulin, antimicrobial agents, irradiation of the lymphoid tissue, physical conditioning and vitamins all have their adherents, but none of these measures has been shown to have a significant effect in reducing the incidence of the common cold.[18]

CONCLUSIONS AND SUMMARY

Epidemiological observations and human transmission experiments have contributed most of what we know about the common cold. They have established with reasonable certainty that it is an infectious disease caused by a filtrable agent or agents, most likely viral, and that its primary mode of transmission is by intimate contact. Little or no immunity develops after infection; however, a relative degree of resistance seems to appear with increase in age. It has also been observed that

there is considerable individual variation in susceptibility to the disease. Although clinical impressions and epidemiological observations have suggested that provocative factors such as exposure to cold, fatigue and others may influence the development of illness, the few experiments that have been conducted to verify these impressions have failed to do so.

In considering measures for the control of common respiratory disease, the available facts are not encouraging. Epidemiological measures—that is, measures designed to interfere with the natural transmission—would seem to offer little. Diseases transmitted through intimate contact are notoriously impossible to control by such an approach.

Immunization of the population as a means of control is an equally discouraging possibility. Since the etiological agent or agents have never been isolated, no specific vaccine can be prepared, and even if this could be done, the failure of an acute illness to confer immunity suggests that vaccination would be equally ineffective.

A highly effective specific therapeutic agent might provide an adequate means of control. However, as yet no such agent is available for the common cold or for any of the other diseases caused by the smaller viruses. Treatment of these perplexing illnesses is nonspecific and consists in making the patient as comfortable as possible and in proper attention to bacterial complications when they occur.

It is obvious that well documented information concerning the common respiratory diseases is fragmentary, indeed. Progress will probably continue to be slow until techniques are found that permit investigators to work with the etiological agents in the laboratory.

The answers to certain questions are badly needed and to a large extent await technical developments. These questions are:

1. Are these illnesses caused by a single agent or multiple agents, and what are their characteristics?
2. Why does no immunity seem to result from infection?
3. What mechanisms determine individual resistance and that associated with aging?
4. What is the importance of latent infection, and are "provoking" factors of any importance?

Finally, the possibility that an effective antiviral agent might be discovered always exists. Certain compounds show some promise in the laboratory, but none has yet proved useful in the treatment of human disease.

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NONBACTERIAL INFECTIONS AFFECTING THE NASOPHARYNX

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Herpangina as a clinical entity was carefully described over 20 years ago (although largely forgotten); it has been re-emphasized as a symptomatic entity since the isolation of Coxsackie viruses in suckling mice and the association of group A Coxsackie viruses with this disease. *Pharyngoconjunctival fever* as such was apparently only rarely recognized until it was described in an outbreak and in sporadic cases in association with type 3 adenovirus (APC, RI virus). *Infectious mononucleosis* is a well described and carefully studied disease the etiology of which, although presumed by exclusion to be viral, is in truth unknown.

HERPANGINA: GROUP A COXSACKIE VIRUSES

Herpangina is a specific infectious disease of summertime, originally described by Zahorsky,[32, 33] that affects chiefly children. The etiology has been established as any of six or seven different group A Coxsackie virus types.[19] Zahorsky[33] reported 82 cases in children from the ages of three to 10 years. Two other outbreaks of illness which was apparently herpangina were reported[1, 16] before Huebner and his associates investigated a group of patients with herpangina and recovered viruses of Coxsackie group A from both throat washings and feces.[12] This was the first indication that a specific virus was a probable cause of the disease. Since then clinical and epidemiological observations have confirmed this etiological relationship.[19]

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ETIOLOGY; EPIDEMIOLOGY

Group A Coxsackie Viruses

Coxsackie is the term applied to a group of viruses first isolated by Dalldorf from two children with poliomyelitis in the town of Coxsackie, New York. These viruses are characterized by their pathogenicity for infant Swiss mice; certain members of the group also are cytopathogenic in tissue culture.[4, 7, 28] Dalldorf proposed the widely used classification into two main groups, A and B.[5] Group A Coxsackie viruses induce flaccid paralysis and marked muscle degeneration, but no significant central nervous system lesions, in suckling mice and cause no apparent disease in adult mice. They may be differentiated in suckling mice from group B Coxsackie viruses, which tend to cause encephalomyelitis, focal myositis, pancreatitis and fat necrosis. The several types within each group are also immunologically distinct. In fact, there would appear to be a clinical distinction between the groups in human beings, group A viruses frequently being associated with herpangina[2, 3, 8, 9, 12, 14, 15, 18, 20, 21, 29, 31] and group B viruses with pleurodynia[11] and aseptic meningitis.[25] At present there are 20 group A Coxsackie virus types,[6] although the majority of reports in the literature refer to types A-1 through A-10.

It is important in assessing data which propose an etiological link between a particular disease entity and group A Coxsackie viruses to recall certain features of these viruses.[19] They are, for example, so prevalent during the summertime that from 1.5 to 7.5 per cent of several groups of well or nonspecifically ill persons tested during the summer were found to be harboring them, particularly those types associated with herpangina. Group A Coxsackie virus infections can occur without inducing observable clinical disease in up to 43 per cent of persons infected. Virus may also persist in the feces for up to 47 days after acute infection. In temperate climates the prevalence is high in the summer and early fall, and children are more often host to these agents than are adults. Fecal material is the commonest source of isolation of virus, although in herpangina the agent may be recovered from saliva, nasal secretions, the oropharynx and stomach washings. For a virus diagnosis the oropharynx and feces are the best sites for sampling.

There is little doubt that family and neighborhood epidemics occur. There is also accumulating evidence that group A Coxsackie viruses spread readily among groups of people under survey, as, for example, in a hospital ward. Because 14 of 33 isolations of group A or B Coxsackie viruses from hospitalized patients were obtained after the ninth hospital day and after there had been two previous negative specimens, it is important that, in evaluating a study for etiological relationships, one know under what circumstances and at what time during a study period

specimens were obtained. These viruses may also be found in the same specimen with other agents, a fact dictating the need for a careful search for other etiological agents if one is tempted to ascribe a non-proved clinical picture to group A viruses.

The clinical association of group A Coxsackie viruses with herpangina occurs more often than would be expected by chance, considering all the factors. In addition, the disease is descriptively distinct enough that it can be recognized by the clinician. The laboratories of the National Institutes of Health have recovered group A Coxsackie viruses from 84 per cent of herpangina patients and 46 per cent of their contacts.[3, 11, 12, 19–21] Group A virus has been isolated from 72 per cent of other reported cases.[2, 8, 9, 14, 15, 18, 29, 31] The virus types consistently have been the same, A-2, A-4, A-5, A-6, A-8 and A-10. Type 3 was found in cases of herpangina in one locale during one season.[2, 3, 8, 9, 12, 14, 15, 18, 20, 21, 29, 31]

There is strongly suggestive evidence that herpangina strains of group A Coxsackie virus cause febrile illness without visible herpangina lesions during the summer. This evidence includes finding virus in family contacts of herpangina patients, when the contacts had only febrile pharyngitis, and also in eight of 13 children with febrile pharyngitis who were not in contact with herpangina cases.[21] In addition, miscellaneous reports by workers throughout the world and several reported laboratory infections lend support to the likelihood that the herpangina strains of group A virus cause febrile pharyngitis and suggestive myositis during the summer.[10, 13, 17, 23, 24, 27, 30, 31] Such illness may be subtypical herpangina and can be diagnosed clinically only when it occurs in relation to cases of herpangina.

Herpangina

The epidemiology of herpangina parallels that of the group A Coxsackie viruses.[1, 3–5, 7, 12, 16, 19, 28] The age distribution is from a few months to adulthood, although half of the cases occur between the ages of one and three and most of the rest from six months to eight years. There does not seem to be a sex difference, and no evidence of difference in race and color. In the Washington, D. C., area 50 per cent of cases occur in July, 35 per cent in August, 5 per cent in June and 10 per cent in September. This incidence is similar in other reports from the temperate climate. Most authors have been impressed with the high infectivity of herpangina, particularly within susceptible family and neighborhood groups.

The high infectivity indicates that the usual mode of spread is probably by excretion of virus from the throat early in the disease and directly from person to person. Virus is also excreted in the feces for

several weeks after infection and might be both a means of acute spread among children and a source of continuing infection. The incubation period appears to be about four days. A permanent immunity seems to follow the infection, although this immunity is apparently type-specific only. Thus herpangina infection, whether clinically manifest or not, can probably occur as many times as there are group A Coxsackie virus types which cause the disease. Several instances of repeated clinical attacks of herpangina are known. Serological studies of neutralizing antibody in adults and the fact that the disease attacks mostly children indicate that immunity is permanent.

CLINICAL MANIFESTATIONS

Clinical descriptions of herpangina associated with group A virus infection correspond strikingly with Zahorsky's reports and with each other.[2, 8, 15, 20, 21, 29]

Table 10 summarizes the clinical features in herpangina.

TABLE 10. *Clinical Manifestations of Herpangina in 68 Cases**

SYMPTOM OR SIGN	
Fever	89%
Duration of fever	2 days (range, 1–4 days)
Convulsions with fever	5%
Anorexia, dysphagia or sore throat	70%
Vomiting	38%
Abdominal pain	21%
Headache	16%

* All cases studied at the Children's Hospital, Washington, D.C., and the virus etiology established in the laboratories of the National Institutes of Health.

The onset of illness is usually sudden and accompanied by fever of 101° to 105° F. in most cases. Cardelle describes diarrhea and myalgia in certain of his patients.[2] In Zahorsky's description, "the child feels tired and often complains of pain in the back and extremities. Headache and pains in the back of the neck are frequently marked symptoms and lead one to expect poliomyelitis at times. This impression is often accentuated by the tenderness of the extremities on movement."

The diagnostic feature of the disease is the presence of characteristic throat lesions. These are gray-white papulovesicular lesions about 1 to 2 mm. in diameter or (their later counterpart) slightly larger ulcers. A zone of erythema surrounds the lesion in most cases. In Zahorsky's description:

> These are . . . vesicles about the size of a millet seed to a small pea . . . on the anterior pillars of the fauces or along the free margin of the soft palate. These vesicles are occasionally discovered on the posterior part of the buccal mucous membrane or

roof of the mouth. Much more frequently the blisters are . . . on the tonsil . . . or on the pharyngeal mucous membrane. The vesicle seems to begin in a small papule which undergoes vesiculation in 24 hours. This often ruptures and leaves an ulcer having a punched out appearance and surrounded by a distinct inflammatory areola about the size of a pea. The ulcer often becomes covered with a thin exudate and its edges are undermined.

The sites of distribution of the lesions in the Children's Hospital study in descending order are the anterior pillars of the tonsillar fauces, the soft palate, the uvula and the tonsils. Usually the lesions are present for four to six days after the onset of illness, and there is an associated diffuse pharyngeal hyperemia in the early stages. A few patients have mild to moderately severe nonpurulent conjunctivitis, and occasional patients have a rash which may not even be directly related to the illness. Although Travassos reports tracheobronchitis in his cases,[29] in general there are no other nasopharyngeal signs or otitis media. The occurrence of herpangina lesions in the vagina with isolation of virus from this site during the course of what otherwise was typical herpangina has been reported.[18]

Total white blood cell counts are under 10,000 in 53 per cent of the cases tested; 20 per cent range from 10,000 to 15,000; and 27 per cent are over 15,000. Cardelle's data show fewer cases with white blood cell counts over 10,000, and no cases with white blood cell counts over 15,000.[2] Cerebrospinal fluid examinations have been performed on at least six children with herpangina and found to be normal. The only apparent lesion, then, is in the oropharynx, although no histological studies have been possible on the lower gastrointestinal tract, where the viruses apparently sojourn for a while and may induce lesions responsible for the abdominal pain.

The only *complications* of herpangina are those already described under the symptomatic picture such as convulsions. The *course* is ultimately benign and the *prognosis* good. *Treatment* does not seem indicated if the diagnosis is correct. Careful bacteriological studies have not shown pathogenic bacteria either early or later in the disease; therefore the use of antibiotics even for prophylaxis does not seem indicated. Antipyretic treatment and attention to other symptomatic therapy seem to be all that is necessary.

The other cases of summer pharyngitis, possibly variants of herpangina, cannot be described specifically, since the characteristic lesion in the oropharynx is absent. However, many cases otherwise fit the general signs and symptoms of herpangina and have been described as "three-day fever,"[30] "acute minor illness"[17] or "febrile pharyngitis."[21]

DIFFERENTIAL DIAGNOSIS

The only clinical condition frequently confused with herpangina is *infectious gingivostomatitis* due to herpes simplex virus.[26] This is a

common childhood illness associated with fever and vesicles or ulcers in the oral cavity, occasionally in the pharynx. Its occurrence is year round; the onset is more gradual than that of herpangina; the age incidence is about the same. The usual symptoms are fever, dysphagia, sore mouth, fetid breath and bleeding gums, which together cause moderately severe illness in the child. Physical findings include cervical lymphadenopathy and hyperemia, hypertrophy and/or hemorrhage of the gingivae with vesiculation and/or ulceration of the gums, tongue, lips and buccal mucous membranes. Fever lasts for three or four days; the oral lesions persist for eight to 14 days. The location of lesions is the most accurate differential point. The presence of ulcerations on the gums, lips, tongue or buccal mucous membrane or of gingival hyperemia, hypertrophy and hemorrhage denotes infectious gingivostomatitis. The presence of anterior pillar or soft palate lesions alone denotes herpangina, but the fact that the lesions were present in these areas in 50 per cent of the gingivostomatitis cases emphasizes the importance of searching the mouth for ulceration before the diagnosis of herpangina is made solely on the basis of pharyngeal lesions.[22]

The differential diagnosis of typical herpangina must also exclude occasional cases of oral moniliasis, infectious mononucleosis, the enanthems of acute exanthematous diseases such as measles, varicella, scarlatina and diphtheria, certain heavy metal poisonings, and deficiency diseases as well as hematological diseases. Apthae of allergic, traumatic and, possibly, psychogenic origin which descriptively appear like herpangina lesions do not usually occur as a part of a febrile syndrome and can usually be differentiated. The febrile phase of other summer infections, including poliomyelitis and group B Coxsackie infections (aseptic meningitis and pleurodynia), may simulate herpangina.

SUMMARY

Herpangina is a specific infectious disease with characteristic throat lesions which should come to the recognition of all physicians caring for children. The etiology is any of several group A Coxsackie viruses. The prognosis is excellent. The importance of this disease lies in the ability of the physician to make the diagnosis, thus allaying the fears attendant upon sudden fevers in children, particularly during the summer.

PHARYNGOCONJUNCTIVAL FEVER

Pharyngoconjunctival fever is a recently defined disease entity characterized by fever, pharyngitis, conjunctivitis and cervical lymphadenopathy associated with infection by the adenovirus type 3.[34, 46] This

virus is one of a group of at least 14 viruses first described in 1953, both as agents resident in human tonsils and adenoids and as viruses associated with acute respiratory disease.[38, 48] They have been recovered not only from tonsils and adenoids, but also from conjunctival, pharyngeal and fecal material and from several internal organs at autopsy. Other names used for this virus group are APC (adenoidal-pharyngeal-conjunctival) virus, ARD (acute respiratory disease) virus and RI (respiratory illness) virus.

ETIOLOGY

The adenoviruses show a unique destructive effect in tissue culture of epithelial tissues, particularly of the serially propagated HeLa cell strain of human cervical carcinoma.[49] The viruses are ether-resistant, heat-labile and filtrable. They resist antibiotics in vitro and in vivo. Members of the group are identified by the presence of a soluble antigen which gives a group reaction in a complement fixation test. This reaction and the unique cytopathogenic effects in tissue culture are the criteria for inclusion of a virus in the adenovirus group. The viruses do produce a type-specific neutralizing antibody in animals as well as in human beings; and on the basis of neutralization tests it can be said that there are at least 12 human and two simian immunologically distinct types of adenovirus.[47]

These viruses have been found in tonsils and adenoids from several parts of the world in up to 90 per cent of specimens tested.[49, 50] Their prevalence is also demonstrated by their being found commonly in association with varying degrees of illness in certain survey groups*, [49] and by the prevalence of neutralizing antibody against them in the various populations tested.[37, 39, 40, 49] In the Washington, D. C., area, for example, tests for neutralizing antibody against adenovirus types 1 through 6 indicated that over 50 per cent of infants in the six to 11 month age group showed evidence of having been infected with at least one type of virus, and by middle adulthood almost all persons showed antibody against at least one type of virus.[49]

All the adenovirus types 1 through 6 have been isolated at one time or another from tonsillar and adenoid tissue, although types 1, 2 and 5 have been found most frequently in pharyngeal lymphoid tissue. Types 1, 2 and 5 were also found in cases of nonspecific febrile pharyngitis in a study of institutionalized children.* Type 3 virus has been associated several times, with good evidence for epidemiological relationship, with pharyngoconjunctival fever,[34, 35, 45, 46] but it has also occurred in a few cases of febrile pharyngitis and in a disease resembling roseola infantum.[44] Type 4 virus, the prototype strain for which is RI-67, has been found in acute respiratory disease and in a primary atypical pneumonia-like illness among military recruits.[34, 37, 39, 40] Type 6 has been isolated from patients with conjunctivitis and mild respiratory symptoms.[41] Type 7 apparently parallels type 4 and its clinical distribution. Type 8 has occurred in

* R. J. Huebner, W. P. Rowe and J. A. Bell: Unpublished data.

cases of epidemic keratoconjunctivitis.[42] Type 10 was found in a case of conjunctivitis simulating trachoma.*, [47] Types 9 and 11 were isolated from feces in a survey of patients with poliomyelitis-like disease.[43] Three additional types have not yet been assigned a specific number; these include one isolated from the feces of a child with Niemann-Pick disease and two isolated from a monkey or a chimpanzee.[47]

The etiological relation of type 3 adenovirus to pharyngoconjunctival fever was demonstrated when a clinical illness associated with this virus occurred in four children and four adults among the patients and staff of a hospital service.[46] The occurrence of an outbreak of similar illness in a summer day camp and, simultaneously, smaller outbreaks or sporadic cases throughout the Washington, D. C., and Leesburg, Virginia, areas enabled clinical, laboratory and epidemiological studies to be made sufficient to establish the etiological relationship.[34] The facts collected included the following: (1) Persons showing clinical illness, from whom virus was isolated, also showed a specific antibody response, indicating that these agents did invade their tissues. (2) Virus was found at the site of the lesion in the clinical entity. (3) Virus was not present in well persons who were in intimate contact with the patients. (4) Virus was present in the acute stage of illness, but not before or after it. (5) Virus was associated consistently with this particular clinical entity. (6) Virus was not found in other illnesses occurring at the same time as the outbreak studied or in sporadic studies of many cases of respiratory or other kinds of illness. Later it was found that swabbing of these agents into the conjunctival sac of human volunteers reproduced essentially the clinical entity of pharyngoconjunctival fever, although spraying of the agent into the nasopharynx did not produce clinical illness even though infection, as evidenced by antibody rise, occurred.

In addition, serum specimens available from an outbreak of conjunctivitis and sore throat described by Cockburn[35, 36] in 1953 showed a specific neutralizing antibody response to adenovirus type 3. A similar outbreak of pharyngoconjunctival fever reported from Canada is also thought to have been associated with type 3 adenovirus infection.[45]

Whether adenoviruses remain latent in the tonsils and adenoids in most persons after acute infection such as pharyngoconjunctival fever has not been established. It is interesting to note, however, that previous to 1954, in which year pharyngoconjunctival fever and type 3 adenovirus infection were prevalent in the Washington, D. C., area, no type 3 virus was found in the tonsils and adenoids from children in the area. The following year type 3 virus was found in the tonsils or adenoids of several children, one of whom had been in the day camp outbreak. One might postulate that after an acute infection with adenoviruses the patient may carry the latent virus for an indefinite time in the pharyngeal lymphoid tissue.

* C. Bogaert and R. H. Parrott: Unpublished data.

CLINICAL MANIFESTATIONS

The illnesses observed in the eight patients in the hospital ward outbreak had the appearance of a distinct nosologic entity with somewhat variable features. Fever for five or six days was observed in six patients. Pharyngitis occurred in seven, with exudate in two.

Seven patients had rhinitis, and one patient appeared to have a common cold. Definite cervical lymphadenopathy was present in five cases, and conjunctival erythema in four. Three patients in this outbreak had transient liver enlargement, accompanied by tenderness in two. Total white blood cell count taken early in the illness in six of eight cases ranged from 7400 to 16,400, with counts higher than 11,000 in four. During the early period of illness there was a slight tendency to neutrophilia; as symptoms progressed differential counts returned to normal, and mild leukopenia developed in most of the patients.

TABLE 11. *Physical Signs of Pharyngoconjunctival Fever*

Fever	90%
Duration of fever	1–10 days (average, 4–6 days)
Pharyngitis	75%
Rhinitis	50%
Cervical lymphadenopathy	75%
Conjunctivitis	75%

In the epidemiologic survey[34] the distribution of symptoms in virus-positive cases was as follows: fever, 90 per cent; sore throat, 70 per cent; red eyes, 66 per cent; headache, 68 per cent; malaise and lassitude, 72 per cent. Symptoms did not vary significantly with age, except for malaise and lassitude accompanied by muscle, bone and joint pain, which were noticed more often in adults than in children. The sore throat was generally mild and usually did not cause difficulty in swallowing. Excess lacrimation with irritation and redness of the eyes was the chief complaint in most instances. Headache was common and was relatively severe in the adults, who also complained of listlessness and drowsiness toward the end of the febrile illness.

The physical signs of pharyngoconjunctival fever are presented in Table 11. Fever ranged from 102° to 104° F.; it was generally nonremitting and subsided by modified lysis. Pharyngitis consisted essentially in lymphoid hyperplasia. Lymphadenopathy was distributed most strikingly in the posterior cervical areas. Many of the children manifested posterior cervical lymphadenopathy two to three weeks after the onset of illness at a time when follow-up serum specimens were being obtained. Rhinitis with rhinorrhea occurred, but was not particularly bothersome. Conjunctivitis was unilateral in a third of the patients. In some instances the conjunctivitis which was unilateral initially, later

became bilateral. Both the bulbar and palpebral conjunctivas were involved, with superficial inflammation manifested mainly by injection of the vessels. There was a great deal of excess lacrimation. Conjunctivitis lasted for a few days to almost three weeks and usually was still present in some form after defervescence. A few patients showed meningismus, and some had cough with rhonchi.

Various combinations of the chief clinical manifestations occurred in the 80 virus-positive cases. For example, fever occurred without conjunctivitis or sore throat in nine cases, with conjunctivitis in another nine cases, with sore throat in 17 cases, and with sore throat and conjunctivitis in 37 cases. Sore throat without fever occurred in one case, and conjunctivitis alone in six cases. Conjunctivitis and sore throat without fever were present in one case.

The clinical studies in the day camp and associated outbreaks were not ideal, nor were all the 80 virus-positive patients examined at several intervals during illness. Thus, in the breakdown of combinations of manifestations, cervical lymphadenopathy was not included, since it was not recorded uniformly by the several members of the epidemiological team. It is the impression of several clinicians associated with the study that lymphadenopathy, particularly in a posterior cervical distribution, was a prominent feature of the illness.

The four main clinical features, then, are fever, conjunctivitis, pharyngitis and posterior cervical lymphadenopathy. If the main features of pharyngoconjunctival fever are present, or a combination of them is present during an epidemic, one can be fairly definite about the diagnosis of type 3 adenovirus infection without having a virological diagnosis.

Complications of pharyngoconjunctival fever were not observed in the summertime outbreak. However, in the ward outbreak and in several sporadic cases which occurred in the winter, signs of paranasal obstruction were observed. Sinusitis and otitis media with prolongation of the fever and leukocytosis were present in one of the children in the ward outbreak.

The *prognosis* in general is good, although patients are quite ill with fever during the course of the disease. The fever in adults is often frightening because of its height and duration.

Neither in the test tube nor in the observed cases has there been any suggestion of response to specific antibiotic *treatment*. Thus, if the diagnosis can be established, treatment need be only symptomatic, unless there is complicating otitis and sinusitis. How extensive the variations in this disease may eventually be is in question. For example, certain patients seemed to have a "common cold"; others showed meningeal signs, but no pleocytosis; some in the hospital outbreak showed liver tenderness and delayed bromsulphalein excretion.

There is a likelihood that it will be possible to immunize human

beings against adenoviruses, although the need for such immunization and its practicality for children remain to be demonstrated.

EPIDEMIOLOGY

Pharyngoconjunctival fever occurs both epidemically and sporadically. The prevalence of the disease is probably defined by the degree of immunity existing in a community or group at risk. It affects persons of all ages, although mostly children, and both sexes, although, interestingly enough, among adult contacts the mothers were more frequently ill than the fathers. It is spread by direct contact almost surely, and probably by respiratory secretions, although virus can be found in feces as well as in nasopharyngeal and conjunctival washings. The fact that, in human volunteer experiments, disease could be induced only when virus was inoculated into the conjunctival sac raises a question as to whether the usual portal of entry is conjunctival or nasopharyngeal. In several instances outbreaks have been associated with swimming pools. The pools may be a factor in the direct spread of this disease, or conjunctival irritation by the water may permit ready ingress for the virus.

The disease is rather highly infectious, as manifest by the fact that about 60 to 70 per cent of all children from birth to nine years of age have been infected in some studies. Persons who do not have the clinical syndrome do not show evidence of infection with the virus. There is both serological and epidemiological evidence of increased immunity with age, there being progressively decreasing attack rates in the older age groups. The incubation period is five to six days; the period of communicability as defined by virus isolation is up to nine or ten days.

DIFFERENTIAL DIAGNOSIS

In its typical form pharyngoconjunctival fever need not be confused with any other known clinical entity. When it occurs as a sporadic case and without a majority of the clinical features, it could obviously be confused with a number of infections. Among these might be pharyngitis due to streptococci and other viruses, including group A Coxsackie viruses, and influenza. *Streptococcal pharyngitis*, at least in older children, is productive of greater erythema and often of exudate on the tonsils, as well as leukocytosis. Group A Coxsackie pharyngitis in its typical form, herpangina, shows vesiculo-ulcerative lesions on the anterior pillars of the tonsils and uvula. *Influenza* usually shows more generalized symptoms and involvement of the respiratory tract than does pharyngoconjunctival fever. It is possible that pharyngitis due to other adenoviruses will emerge with the clinical picture of pharyngoconjunctival fever.

As a cause of conjunctivitis with fever, *leptospirosis* might enter the differential diagnosis, but is considerably less common and usually produces generalized symptoms. There are other causes of *conjunctivitis*, including other adenovirus types, which may need to be differentiated from pharyngoconjunctival fever. The described cases of epidemic keratoconjunctivitis and inclusion conjunctivitis are usually of greater duration and often cause corneal involvement, and the latter may upon examination of scrapings show inclusions. None of these features was present in pharyngoconjunctival fever. In addition, no bacterial organisms such as *Hemophilus influenzae* were regularly isolated.

SUMMARY

Pharyngoconjunctival fever is a recently recognized communicable disease characterized by fever, pharyngitis, conjunctivitis and cervical lymphadenopathy, alone or in combination. A newly discovered virus, adenovirus (APC) type 3, is etiologically related to it as shown in clinical, laboratory and epidemiological studies. The disease can be diagnosed clinically when all the characteristic features are present or when it occurs in an epidemic form even though not all the main manifestations are present.

INFECTIOUS MONONUCLEOSIS

Credit for the original description of infectious mononucleosis is usually ascribed to Filatov, who in 1885 reported several cases of cervical lymphadenopathy of obscure etiology.[70] Four years later Pfeiffer described similar cases and applied the name "glandular fever" to what he felt represented a specific entity.[99] In 1909 Burns reported several patients with "glandular fever," six of whom were children.[59] He emphasized the increase of "mononuclear" cells during the course of the disease as well as the leukocytosis that may occur. This was confirmed by Deussing a few years later.[64] In 1920 Sprunt and Evans commented on the mononuclear lymphocytosis occurring in "glandular fever" and suggested that the disease be called "infectious mononucleosis."[108] The name "infectious mononucleosis" had been used earlier by Baetzer in the discussion of a paper presented in 1915.[83] In 1923 Downey and McKinlay drew the attention of investigators to the study of detailed cytology in this disease.[66] They described and illustrated three types of abnormal lymphocytes found in infectious mononucleosis, all of which could be differentiated from leukemic cells. Paul and Bunnell[98] in 1932 were the first to describe the heterophile agglutination test for the diagnosis of infectious mononucleosis, which represented the first clinical usefulness of the heterophile antigen-antibody response described in detail by Forssman[71] in 1911. Papers on infectious mononucleosis since 1932 have dealt variously with the protean manifestations of the disease, the pathology, the etiology, the criteria for diagnosis and the epidemiological aspects.

INCIDENCE

The early literature emphasizes the occurrence of infectious mononucleosis in children. Tidy and Morley[110] calculated that about 80 per

cent of the cases reported up to 1921 were in patients under 13 years of age. Later reports,[56, 75] however, assert that the disease occurs most frequently between the ages of 15 and 30. Generally, then, it is a disease which is seen for the most part in childhood and young adult life, although cases in infants and elderly adults have been reported.

It is difficult to establish any seasonal incidence. The reported epidemics, however, have been for the most part in the spring and fall.

ETIOLOGY; PATHOGENESIS

It is generally accepted that infectious mononucleosis is a specific entity of probable viral etiology, although the agent has never been identified. In support of this hypothesis are the many reports of epidemic outbreaks of this disease.[104] In opposition, it may be pointed out that most cases occur sporadically, that they rarely develop in close contacts of the patients,[69, 79] and that certain reports of epidemics can be attributed to insufficiently rigid diagnostic criteria.

In attempts at transmission of the disease to human volunteers or laboratory animals, unequivocal evidence of successful transmission was not obtained, although a few human and monkey subjects[67, 68, 88, 107, 114] showed suggestive clinical or hematological signs of disease. Attempts to isolate a virus from throat washings or stool suspensions in tissue culture using monkey kidney, HeLa and human embryo fibroblast cells have been unsuccessful in our laboratory.

Listeria monocytogenes, a small, gram-positive motile rod, has been considered a possible cause of infectious mononucleosis[77] because it has been isolated from the blood and cerebrospinal fluid of patients presumed to have the disease.[95, 100, 105, 113] Wising, however, failed to isolate the organism from excised lymph nodes.[114] Most investigators have been unable to demonstrate any rise in antibodies against *Listeria monocytogenes* in serums of convalescing patients.[85, 87, 109, 114]

Although beta hemolytic streptococci have occasionally been cultured from the throats of patients with infectious mononucleosis, it seems most likely that this represented a complicating infection masked by the signs and symptoms of the primary disease.[53]

PATHOLOGY

The lesions in infectious mononucleosis are as various as are the clinical manifestations.

The first to describe specific histological findings in the *lymph nodes* were Gall and Stout.[74] They emphasized that although the architecture of the node may be distorted, it is not destroyed. They observed the proliferative activity in the pulp which tends to obscure the margins of the follicles; the focal proliferative activity of clasmatocytes which

simulate "epithelioid cells"; and the appearance throughout the pulp, on the edges of the germinal centers, and in the sinuses of large numbers of "specific infectious mononucleosis" cells.

The most complete report of the pathological picture in infectious mononucleosis appeared in 1948.[60] The material included nine autopsies and many specimens of biopsy material. Four of the patients died as a result of "spontaneous" splenic rupture. Development of the Guillain-Barré syndrome accounted for the death of two additional patients. Nasopharyngeal hemorrhage and laryngeal edema each caused one death. The last patient died of an unrelated accident.

The *spleen* is invariably enlarged during the course of the disease. The capsule shows varying degrees of infiltration with both normal and abnormal lymphocytes, which appear to cause its dissolution and may explain the occasional spontaneous rupture. The internal structure of the spleen is likewise often distorted because of cellular infiltration and hyperplasia.

The *bone marrow* usually appears grossly normal except for the presence of atypical cells such as those found in the peripheral smear. Hyperplasia, if present, is usually limited to the granulocytic series. Marrow studies in patients who have purpura exhibit "an increase in megakaryocytes which show greatly diminished platelet production."[61]

The most prominent lesion of the *respiratory system* is lymphoid hyperplasia in the nose and throat. Ulceration of this hyperplastic tissue may occur, and secondary bacterial infection may develop locally.[60] This process in the nose may lead to epistaxis. Varying degrees of mononuclear cell infiltration of the larynx and trachea have been described.[60] Pneumonia, if present, is of the interstitial variety characterized by mononuclear cell predominance.[60, 101] Aggregates of lymphocytes may be found in the myocardium beneath the endocardium and in the pericardium.[51, 60, 86] Myocarditis may be severe enough to cause death.[86]

There may be increased numbers of lymphocytes in the wall of the *stomach* and *intestine*. The *liver* is enlarged in the more severe cases. Microscopically, there is a periportal lymphocytic infiltration of differing degrees which is hardly distinguishable from the milder cases of viral hepatitis. There may be loss of liver cells in the periphery of heavily infiltrated areas.[60] Perivascular lymphocytic collars may be seen in the pancreas, but the parenchyma of the organ remains normal.

The *renal* lesion of infectious mononucleosis is essentially an interstitial nephritis.[60] The lesions are largely confined to the periphery of blood vessels, but aggregates of lymphocytes are also found in the interstices of the cortex.

Involvement of the *nervous system* includes edema and congestion of the meninges with mononuclear infiltration. Perivascular hemorrhages as well as ganglion cell degeneration have been observed. The anterior nerve roots and myelin sheaths may also show collections of lymphocytes.

Similar infiltrative lesions have been described in the adrenals, pituitary glands, testes, bladder, muscles and corium.

CLINICAL MANIFESTATIONS

The most common presenting complaint is low grade fever.[73] It usually lasts from seven to 21 days and is characterized by morning remissions. Sore throat may or may not be present initially. General symptoms, including malaise, chills and sweats, headache, dizziness or faintness, retro-orbital aching, and irritability, may be present. Other early symptoms include neck pain, abdominal pain and arthralgia.

Sore throat is the next most common single manifestation of this disease. It may precede the disease, occur during its course or become evident toward the end of it. It may manifest itself as a diffusely erythematous pharynx (34 per cent), as a follicular tonsillitis or pharyngitis (40 per cent), as an ulcerative pharyngitis (19 per cent) or as a membranous pharyngitis (7 per cent).[56]

Although the cervical lymph nodes are usually the first to enlarge, there is generalized lymphadenopathy in 70 per cent of patients.[75] This may occur early and in fact be the presenting complaint, or it may become manifest at any time during the course of the disease. The duration of enlargement varies from a few days to several months.

The reported incidence of splenomegaly varies from 20 to 64 per cent.[56, 73] The organ is usually palpable by the end of the first week of illness and may remain enlarged for a variable time. The spleen may be enlarged in the absence of significant lymphadenopathy.

Rashes are seen in up to 20 per cent of cases. The skin eruption is usually patchy and localized principally to the trunk. The rash is ordinarily discrete and macular, but may be morbilliform, vesicular or petechial. It is most common during the first week of illness. A petechial enanthem may be seen on the soft palate early in the disease, but is certainly not specific for infectious mononucleosis.[81]

Five to 10 per cent of patients with infectious mononucleosis show clinical jaundice, which is often transient, during the first or second week of illness. Over 80 per cent may show aberrations of commonly used liver function tests.[82]

Central nervous system manifestations during infectious mononucleosis occur more commonly in older patients, but also in children.[57, 80, 89, 112] There may be disorientation, meningeal signs, a Guillain-Barré type of syndrome, Babinski response and even diminished sensation. One reported case presented with a grand mal seizure.[106] On the other hand, the patient may have no symptoms or signs of nervous system involvement, but yield cerebrospinal fluid with increased mononuclear cells and with or without an increase in protein.

The neurological complications are most frequent between the first and third weeks of illness.

Involvement of other organ systems may cause confusion in establishing the diagnosis. The heart may show changes indicative of either pericarditis or myocarditis. Hematuria secondary to thrombocytopenic purpura or to infiltrative lesions is present in a small percentage of cases. Complaints of arthralgia are frequent, although objective signs of joint disease have not been documented. Involvement of the eyes as manifested by conjunctivitis, retro-orbital pain, photophobia and swelling of the eyelids may be present.

LABORATORY DATA

Hematology

The lymphocytes occurring in infectious mononucleosis were described by Downey and McKinlay[66] as three different atypical cell types, although they admitted that there was so much gradation between the types that this differentiation was theoretical. The cells are predominantly type I, are characteristically much larger than a mature lymphocyte, and contain a basophilic cytoplasm which is excessively vacuolated. The nuclei of the larger cells are frequently placed eccentrically and generally are irregular or indented.

Although these atypical cells appear in almost 100 per cent of reported cases, they are not specific for infectious mononucleosis. They may occur in many viral diseases such as measles, atypical pneumonia, viral hepatitis, herpes zoster, respiratory viral disease and herpes simplex. Atypical lymphocytes have also been reported in toxoplasmosis.

Lymphocytosis of 50 per cent or greater may occur as early as the second day of illness, and over 80 per cent of the patients will show this type of peripheral blood picture before the end of the first week of illness.[78] The duration of the lymphocytosis and the presence of abnormal lymphocytes varies from 16 to 106 days, and persistence for even longer periods has been reported.

During the first week of illness the total white blood cell count may be normal or low,[73, 76, 91] but it usually increases during the second week to levels betwen 10,000 and 20,000 cells per cubic centimeter, or occasionally higher.

The sedimentation rate is mildly increased during the course of the disease in up to 50 per cent of patients.[78]

Purpura is occasionally seen and can be explained on the basis of platelet deficiency. Patients with this disease may show drops in their platelet counts without manifesting an overt bleeding tendency.[96] Some patients have been reported who also had depression of cells in the white and red cell series.[51]

Acute hemolytic anemia is another complication that may occur.[58]

Serological Considerations

In 1911 Forssman[71] described an antigen-antibody reaction in which the antibody may react with an antigen different from, and phylogenetically unrelated to, the antigen instrumental in its production. In 1932, quite by chance, Paul and Bunnell[98] found that patients with infectious mononucleosis had antibodies that would agglutinate or hemolyze suspensions of sheep red cells. These antibodies could be differentiated from those occurring in the serums of otherwise normal persons or patients with serum sickness only by differential absorption studies using guinea pig kidney and beef erythrocytes. The differentiating characteristics are given in Table 12.

TABLE 12. *Heterophile Antibody Absorption Tests*

TYPE OF SERUM	ANTIBODY ABSORPTION BY GUINEA PIG KIDNEY	ANTIBODY ABSORPTION BY BEEF ERYTHROCYTES
Normal	Yes	No
Infectious mononucleosis	No	Yes
Serum sickness	Yes	Yes

From Davidsohn.[62]

There is much controversy over what should be considered a significant titer. This will of course vary with different modifications of the test. In a series reported by Leibowitz[91] 200 normal adults were tested, and none had titers exceeding 1:56. Titers up to 1:448 may be found in virus hepatitis, tuberculosis, sarcoma, polycythemia, leukemia, Hodgkin's disease and atypical pneumonia. These antibodies on differential absorption tests usually prove to be of the normal Forssman type. Leibowitz feels that in the absence of serum sickness a titer of 1:1792 or higher is diagnostic without the aid of absorption characteristics.[91, 92] In titers lower than this he feels that the absorption studies should be performed. Most authors feel that the diagnosis is secured by the demonstration of a titer of 1:56 or greater with unabsorbed serum or a titer of 1:28 after absorption by guinea pig kidney. Evidence of a rise in titer on paired serums from early and late in the disease with appropriate clinical and hematological findings is more conclusive.[52, 73, 76, 78] Most authors feel that well over 90 per cent of patients will show positive heterophile agglutination tests.

The titer starts to rise in the first week of illness and reaches its peak between the first and third weeks. If the test is not positive by the end of the second week, other diagnoses should be sought.

Miscellaneous Tests

Liver function tests are altered in 40 to nearly 100 per cent of cases.[82, 91] Since liver function tests reflect either relative changes of the various protein fractions or actual quantitative differences, and since the liver is important in protein metabolism, it is reasonable to believe that that organ is directly involved in the disease process.

When there is central nervous system involvement, the *cerebrospinal fluid* generally shows less than 200 cells per cubic centimeter with a preponderance of mononuclear cells.[106] The protein may be elevated. The sugar is not altered.

Roentgenograms of the *chest* may reveal enlargement of mediastinal lymph nodes, with or without parenchymal infiltration.[93]

Electrocardiographic abnormalities may be present without obvious clinical involvement of the heart.[94] The changes are for the most part indicative of pericarditis, but myocarditis may also occur. The abnormalities include T wave inversion in the precordial leads, slight depression of the RS-T segments, minor arrhythmias, and disturbances in atrioventricular conduction.

Hematuria is occasionally seen and may be due to either thrombocytopenia or actual nephritis.

PROGNOSIS

The average patient is symptomatic for about two weeks.[55, 78] What has been termed a chronic form of infectious mononucleosis has been reported, but the presence of atypical lymphocytes in the blood coupled with chronic complaints was the only basis for this description.[84] It is true, however, that the serological and hematological abnormalities may be present for several months in patients who are asymptomatic.

Recurrent infectious mononucleosis has been reported.[97, 102] The diagnosis during the second episode was supported by a positive Paul-Bunnell test as well as by the presence of atypical lymphocytes and compatible clinical findings.

Although a mortality rate between 1 and 2 per cent was reported in 1940 in a series of 500 patients,[90] current experience and a review of the literature do not seem to confirm this high rate.

DIFFERENTIAL DIAGNOSIS

To make the diagnosis of infectious mononucleosis, one needs the characteristic serological, hematological and clinical findings already discussed.

Leukemia, infectious lymphocytosis and idiopathic thrombocytopenic purpura may at times be confused with this disease. However, in all three diseases the heterophile agglutination test is negative.

The rash and lymphadenopathy of infectious mononucleosis often simulate German measles. The lymphadenopathy alone can be confused with conditions of much more severe prognosis such as Hodgkin's disease.

The tonsillitis which is often present may be difficult to distinguish from that due to group A beta hemolytic streptococcus.

There is a striking resemblance between *infectious hepatitis* and infectious mononucleosis both clinically and in laboratory findings. The gastrointestinal symptoms usually are predominant in the former, and the anginal symptoms in the latter, but this is not always true. To add to the confusion, atypical lymphocytes may be present in infectious hepatitis. Further, some patients with viral hepatitis have slightly elevated heterophile agglutination tests.[91] Here differential absorption is helpful.

There are several diseases which clinically may be similar to infectious mononucleosis. These include tuberculosis, brucellosis, tularemia, cat scratch fever, typhoid fever, scarlet fever and rheumatic fever.

Acquired toxoplasmosis so closely simulates infectious mononucleosis clinically that it should always be considered in any suspected case of infectious mononucleosis with a negative heterophile agglutination test.

When there is central nervous system involvement, one must consider all the causes of nonbacterial meningitis.

Lastly, it is well to note that patients with infectious mononucleosis may have falsely positive Wassermann and/or Kahn reactions.[103]

TREATMENT

There is no specific therapy for infectious mononucleosis. As in any other acute illness, bed rest is recommended as long as the patient is symptomatic. This should be rigidly enforced in those patients with greatly enlarged spleens to prevent accidental rupture of that organ.

It is the consensus that antibiotics have no influence on the course of the disease.[111] Since secondary bacterial complications seem to be uncommon in infectious mononucleosis, it appears that antibiotics are seldom indicated.

Cortisone and ACTH have been used strictly on an empirical basis with encouraging but occasionally conflicting results.[54, 65] The steroids hardly seem indicated in a self-limited disease such as infectious mononucleosis.

Adequate diet and supplemental vitamins are important considerations in therapy, especially if there is clinical evidence of hepatic dysfunction.

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Pharyngoconjunctival Fever

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Infectious Mononucleosis

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BACTERIAL INFECTIONS OF THE NASOPHARYNX

With Particular Reference to the Prevention of Rheumatic Fever and Glomerulonephritis

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Although the human nasopharynx is the transient residence of a number of pathogenic bacteria, only two bacterial agents, the group A streptococcus and the diphtheria bacillus, are clearly capable of causing clinically apparent infection in this area. Moreover, the diphtheria bacillus, though establishing a foothold on nasopharyngeal mucous membranes, produces its main pathogenic effects by systemic toxemia and by obstruction of the lower respiratory tract.

Our knowledge of the pathogenesis of pneumonia, otitis media, laryngotracheobronchitis and meningitis indicates that organisms such as the pneumococcus, *Hemophilus influenzae* and the meningococcus may be isolated from cultures of the nasopharynx during the development of these infectious processes. Little information is available concerning the degree of invasion of the nasopharyngeal tissues in such infections. It is the opinion of some clinicians that pneumococci, staphylococci and *H. influenzae* produce primary nasopharyngitis. The evidence in support of this belief is meager, and in most instances secondary invasion by these organisms has been conditioned by a preceding viral infection or obstruction with alteration in physiological nasopharyngeal function.

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DIPHTHERIA

Diphtheria in the past two decades has become an uncommon disease as a result of the widespread practice of immunization with toxoid. However, in view of the seriousness of diphtheria in children, the physician must remain alert in order to recognize its sporadic occurrence in the unprotected or inadequately immunized child. Careful clinical evaluation supported by confirmatory bacteriological evidence is necessary to diagnose clinical diphtheria and differentiate it from hemolytic streptococcal infection.

Membranous exudate beginning on the tonsils is the most common clinical sign of diphtheria. Primary involvement of the nasal mucous membrane also occurs frequently in children. The exudate, typically, is white or gray. It is more widespread than the exudate seen in streptococcal tonsillitis and pharyngitis, often becoming confluent over the tonsils and extending to the surrounding tissues. Extension to the nasal mucosa and to the larynx frequently occurs. Diphtherial exudate is more adherent to the mucous membrane than streptococcal exudate, and removal often causes bleeding of the underlying surface. Infrequently, diphtheria may occur without membranous exudate or with exudate that is follicular or punctate;[12] this is sometimes seen in the incompletely immunized patient. In contrast to streptococcal pharyngitis, there is little injection of the pharyngeal mucosa in diphtheria. The throat is not usually sore, nor is there pain on swallowing. Diphtheria differs from streptococcal infection in having a more insidious onset, but it may progress to a far more serious illness when toxemia becomes full-blown.

Material swabbed from the diphtheritic membrane and inoculated on Loeffler's medium provides a rapid and efficient method of bacteriological diagnosis. Swabs streaked on this medium at the bedside are easily transported, and a trained bacteriologist can identify typical morphological forms of *Corynebacterium diphtheriae* in smears made from Loeffler's medium after eight to 12 hours' incubation.

If diphtheria is suspected on clinical grounds, treatment with antitoxin should be started before cultural results are obtained. Antitoxin appears to have no neutralizing effect upon toxin that has been fixed to tissue, so that delay in therapy may permit rapid progression of the disease. Antibiotic therapy, though without effect on the toxemia of diphtheria, does appear to be of value in the eradication of the organism and in the treatment or prevention of complicating streptococcal infection. Penicillin has been extensively used for this purpose; it should be given in full therapeutic doses for at least 10 days.

STREPTOCOCCAL INFECTION

Infection of the nasopharynx by the group A streptococcus represents the most common form of bacterial disease of the upper respiratory tract.

Streptococci causing human disease[10] produce complete, clear-zone hemolysis on blood agar plates. The serological classification of these organisms into groups is determined by the reaction of a polysaccharide in the streptococcal cell wall with specific antiserum. Most human infections are caused by group A streptococci; organisms of groups C and G only rarely infect man. Type-specific M protein, a surface antigen of group A streptococci, is the basis of the subdivision of members of this group into more than 40 specific types. The M antigen, apparently by virtue of its ability to interfere with phagocytosis, is primarily responsible for the virulence of group A streptococci. Type-specific antibody directed against the M protein is the main factor in the acquisition of immunity to streptococcal infection. As a result of the specificity of this relationship, multiple infections by different M types of group A organisms can and frequently do occur in man.

A number of other extracellular and intracellular substances have been identified as components of the group A streptococcus. Of these, only the erythrogenic toxin responsible for the rash of scarlet fever has a known role in the pathogenesis of streptococcal disease. However, several antigenic extracellular substances, streptolysin O, streptokinase, streptococcal hyaluronidase and desoxyribonuclease, are elaborated by hemolytic streptococci in vitro and in vivo when human tissues are infected by these organisms. Titration of antibody formed as a result of parasitism is of value in confirming the occurrence of streptococcal infection. For this purpose the antistreptolysin test is usually performed.

Clinical Characteristics of Infection

In children, disease produced by the group A streptococcus shows a wide variation in clinical pattern. In the older child, as in the adult, streptococcal pharyngitis usually begins with the sudden onset of sore throat. This is accompanied by constitutional symptoms including fever, chilliness, headache and malaise. The patient complains of pain on swallowing. The throat is diffusely reddened, but with extensive edema it may appear pale. The uvula is often edematous, and edema of the tonsils and pharynx is also seen. Lymphoid tissue of the posterior pharyngeal wall is frequently hyperplastic, and sticky, mucopurulent postnasal secretions are often adherent to the posterior pharyngeal mucosa. In 60 to 80 per cent of patients, patches of white or grayish-yellow exudate dot the tonsils, frequently the pharyngeal mucosa, and may become confluent over the tonsils. Exudate is less likely to be seen

during the first 24 to 36 hours of the illness. The cervical lymph nodes are usually enlarged and tender to palpation. The total leukocyte count is elevated, and culture of the inflamed tonsils or pharynx, if no antibiotic has been given, shows many colonies of hemolytic streptococci.

Streptococcal illnesses in younger children are less typical. Profuse nasal discharge with excoriation of the nares is more frequent. Nausea and vomiting occur and are often accompanied by abdominal pain. A mild cough may develop. Systemic manifestations are more prominent and of longer duration. Suppurative complications frequently develop. The inflammatory reaction in the pharynx is not as intensive, and exudate is less frequently seen.

Boisvert and Powers[13] proposed a clinical classification of streptococcal infections based on differences in symptomatology that appear to occur with increasing age. According to their description, illnesses in infants under six months of age are characterized by irregular low grade fever, anorexia, vomiting and a mucopurulent nasal discharge with excoriation of the nares. Symptoms continue for about one week. The type of illness occurring in children from six months to three years of age is more severe. The onset is insidious, and irregular low grade fever may persist for several weeks. Mild inflammation of the pharynx without exudate and a more purulent anterior and posterior nasal discharge are seen. Anorexia, vomiting, irritability and loss of weight are noted. Suppurative complications such as otitis media, cervical adenitis, pharyngeal abscesses and pyodermia often occur. In the intermediate age group, from three to 10 years, streptococcal infections are more localized. Nasopharyngitis and tonsillitis frequently without exudate are seen. Suppurative manifestations are less common, but scarlet fever often occurs.

The presence of the typical rash of scarlet fever is helpful in the diagnosis of streptococcal infection. It appears as a diffuse, finely papular, erythematous eruption, more prominent in fair-skinned persons. It begins about the base of the neck, in the axillae and groins, and spreads to the trunk and the extremities. When the eruption is intense, small miliary vesicles may appear on the trunk, and scattered petechiae may be seen. The skin is roughened; this is a helpful diagnostic sign in races with heavily pigmented skin. The rash is due to hyperemia, and pressure causes it to fade. In addition to the exanthem, a characteristic buccal and pharyngeal enanthem is seen. The mucous membranes are intensely reddened; this injection may appear punctate over the palate. The tongue is initally coated; then the edges become swollen and red; later it becomes completely desquamated, leaving a beefy-red surface with swollen papillae—the so-called strawberry tongue.

In addition to scarlet fever, the nonsuppurative sequelae, rheumatic fever and glomerular nephritis, may complicate streptococcal infections

of the intermediate and adult types, whereas they rarely follow infections of the childhood type.

The principal manifestations of streptococcal illnesses in more than 900 pediatric patients in the group studied by Boisvert and Powers at the New Haven Hospital during 1934–6 (before sulfonamides), during 1938–40 (after the introduction of sulfonamides) and during 1948–50 (after antibiotics came into use) are listed in Table 13. It is interesting to note a decreased incidence of suppurative complications, including otitis media, cervical adenitis, pharyngeal abscesses, pyodermia, erysipelas and bacteremia after the introduction of chemotherapy.

TABLE 13. *Clinical Manifestations of Streptococcal Infection in Children*

PRINCIPAL MANIFESTATION	PER CENT OF CASES				
Nasopharyngitis					
Tonsilitis.....16	34	46	40	78	
Scarlet fever.....11	25	8		13	
Otitis media.....15	14	9	32	5	
Cervical adenitis..... 7	5	1	6	3	
Other suppurative manifestation.....51	22	36	22	1	
Source	Powers 1934–6*	Powers 1938–40*	Powers 1948–50*	Rantz 1947—†	Breese 1947–52‡

* Modified from Curnen and Powers in Grulee and Eley: *The Child in Health and Disease*. 2nd ed. Baltimore, Williams & Wilkins Company.

† Modified from Rantz et al.[16]

‡ Modified from Breese.[2]

Rantz, in a study[16] of approximately 100 patients 0 to eight years of age seen in the children's clinic of the Stanford University Hospitals since 1947, obtained results similar to those reported by Boisvert and Powers. The variations in clinically recognized streptococcal infections observed are presented in Table 13. A breakdown of these percentages into two age groups, 0 to four years, and four to eight years, shows that 18 per cent of the cases in the 0 to four year group were classified as streptococcal nasopharyngitis, 47 per cent as otitis media, 7 per cent as cervical adenitis, and 27 per cent as other suppurative manifestations. Corresponding percentages for the older group were 67 per cent nasopharyngitis, 12 per cent otitis media, 6 per cent cervical adenitis, and 22 per cent other suppurative forms. This distribution supports the view that infection limited to the nasopharynx is more characteristic of the older age group.

A description of streptococcal infection seen in a private pediatric practice has been reported by Breese. Data on approximately 1200

streptococcal illnesses seen in Rochester, New York, from 1947 to 1952 are summarized in Table 13; Breese also presents the occurrence of various clinical signs and symptoms seen in these patients.[3] In this study more than 70 per cent of clinically evident infections from which hemolytic streptococci were cultured were classified as streptococcal sore throat. Suppurative manifestations were present in less than 10 per cent of cases. The majority of patients were from three to eight years of age. It was estimated that in 12 to 44 per cent of culturally positive illnesses a diagnosis of streptococcal infection was not suspected clinically. The percentage of error increased with decreasing age.

Increasing awareness of the existence of atypical and subclinical streptococcal illnesses has come with evidence acquired by cultural and serological investigations of families, orphanages, schools, hospital wards and military units. From studies of young adults, in whom the diagnostic error should be minimal, it has been estimated that nearly 20 per cent of streptococcal infections may be asymptomatic.[14]

In view of the wide spectrum of streptococcal illnesses, it is difficult to estimate the total incidence of streptococcal disease. In a study of families in Cleveland,[8] streptococcal infections accounted for about 2.5 per cent of respiratory illnesses. Other investigators estimated the incidence in groups they have observed to approach 10 per cent.[1, 6] However, epidemics have been reported in which as much as 40 per cent of a population experienced streptococcal infection.[9]

In addition to keeping the possibility of atypical and asymptomatic streptococcal infection in mind, the alert physician must be aware of other infections in which exudative lesions occur. Pharyngitis with exudate is found in infectious mononucleosis, herpes simplex, Vincent's angina and in nonbacterial exudative pharyngitis as well as in diphtheria. The presence in the blood of abnormal lymphocytes and of agglutinins against sheep red cells in *infectious mononucleosis*, and the finding of typical vesicles as well as exudative lesions in *herpes*, help to differentiate these conditions from streptococcal infection. *Vincent's infection* is insidious in onset; constitutional symptoms and fever are rare. The lesion may be unilateral and have little surrounding inflammatory reaction. In *nonbacterial exudative pharyngitis* the exudate is usually sparse, consisting of small, almost pinhead-sized spots. However, in children the exudate may be confluent and the diagnosis can be ascertained only by laboratory tests; the leukocyte count is normal, and no streptococci can be isolated on culture. Hoarseness and cough usually accompany these nonbacterial infections. The invasion of focal areas of denuded mucosa by organisms such as staphylococci and influenza bacilli, following herpetic infection and infectious mononucleosis, is partially responsible for the impression that these organisms can sometimes cause primary nasopharyngitis.

Laboratory Diagnosis

Two simple laboratory procedures have been of particular help in confirming the clinical diagnosis of streptococcal infection. These techniques, the total leukocyte count and the throat culture, can be performed at the bedside with a minimum of equipment and provide results quickly with little technical effort or expense. In children with streptococcal infection the total white blood cell count is usually 12,000 or more, and the percentage of polymorphonuclear cells is increased. In nonbacterial infections of the throat the total count may sometimes be moderately elevated, but in a streptococcal illness a low count is unusual.

The throat culture is a helpful aid in the diagnosis of streptococcal infections. In some localities municipal and hospital laboratories will provide diagnostic bacteriological service. Some physicians have provided themselves with swabs, a small incubator and blood agar plates, and after a two- or three-visit refresher course at a good clinical bacteriological laboratory have made and read their own culture plates for streptococci. They find the bacteriological identification of hemolytic streptococci fully worth the time expended.

In taking cultures, to obtain best results the swab should be firmly rubbed over both tonsillar areas and the posterior pharyngeal wall and should be inoculated on blood agar within one hour. For house calls, several plates in the physician's bag make this a simple procedure. Infusion agar base containing 5 per cent sheep blood provides the best results; agar plates may be stored in the refrigerator for three or four weeks without deterioration. Group A streptococci produce clear-zone hemolysis, easily differentiated from the greenish, incomplete hemolysis that characterizes *viridans* streptococci, on sheep blood agar. *Hemophilus hemolyticus*, the colonies of which may be confused with hemolytic streptococci, grow poorly if at all on this medium.

In inoculating plates, the swab should be rubbed with a rolling motion over a small area of the agar surface. Then material from this area should be spread over the surface of the agar with a bacteriological loop so as to obtain isolated colonies. Stabbing into the agar with the loop provides adequate subsurface growth so that some hemolytic streptococci that produce better hemolysis under reduced oxygen tension can be detected.

The finding of hemolytic streptococci[10] in the throat does not constitute unequivocal evidence of the presence of streptococcal infection. Small numbers of hemolytic streptococci of groups C, D and G may be found in the normal human pharynx. Organisms of groups C and G have been described as causative agents of pharyngitis in man, but this is an unusual occurrence. Infections caused by these organisms do not appear to result in rheumatic fever or acute glomerulonephritis. Various degrees of transient carriage of group A streptococci in the nasopharynx may occur without being associated with frank infection. Also, the carrier state may be found for weeks or months in a person after a streptococcal illness that was inadequately treated.

Under ideal circumstances, organisms from colonies of hemolytic

streptococci should be grown in pure culture and classified by serological methods into group and type so that their identity as pathogens can be unqualified. Demonstration of an increase in streptococcal antibody in serial serum specimens obtained from a patient from whom group A organisms have been isolated firmly establishes the fact that infection has taken place. This is usually done by determining the titer of antistreptolysin O in acute and convalescent serum specimens; a two-dilution rise in titer is considered significant. Practically, however, the number of colonies found on the blood agar plate is indicative of the presence or absence of infection; heavy or predominant growth strongly suggests infection, whereas a few colonies are more characteristic of the transient or persistent carrier.

Treatment

The effectiveness of an agent in the treatment of acute streptococcal infection should be judged from three viewpoints: amelioration of symptoms, prevention of suppurative complications and eradication of the organism. Since the introduction of the sulfonamides, extensive experience with these drugs has demonstrated that they limit the activity in vivo of group A streptococci to the extent that suppurative complications do not develop, and they improve the clinical course of the acute uncomplicated illness. These agents are effective in the treatment of erysipelas, peritonitis, lymphangitis and bacteremia. However, the sulfonamides do not eradicate group A streptococci from the nasopharynx. Therefore the patient treated with these drugs often becomes a carrier for weeks or months, and through his ability to transfer his organism he may be a source of secondary infection to others. During World War II, following the extensive use of sulfonamides during epidemics of streptococcal infection, strains of group A organisms resistant to sulfonamides appeared.[10] However, the introduction of penicillin prevented this from becoming a serious situation, and sulfonamide-resistant group A streptococci have not been a problem of practical importance since that time.

Penicillin is the drug of choice in treating group A streptococcal infections. Therapeutic doses administered early and maintained for 10 days exert a favorable effect on the clinical symptoms of streptococcal illnesses, prevent the development of suppurative complications, and eradicate the organism from the nasopharynx. However, in the presence of suppurative complications this agent should not be relied upon alone for therapeutic effect. Surgical drainage, when indicated, should be performed, and the possibility of mixed infection with a penicillin-resistant organism should be considered so that repeated cultures should be taken and other antibiotics given when necessary. Penicillin

may be given as the aqueous preparation or in the depot form. Depot type will usually provide adequate therapeutic levels and necessitate fewer injections. Procaine penicillin, 300,000 units per day for 10 days; procaine penicillin with 2 per cent aluminum monostearate, 300,000 units every three days for three doses; and benzathine penicillin, one injection of 600,000 units, are recommended therapeutic programs for the treatment of streptococcal pharyngitis and tonsillitis. Benzathine penicillin, though more convenient, is somewhat more painful than the other preparations. Buffered oral penicillin may be given in doses of 250,000 units three times a day for 10 days. Although the trauma of injection is avoided by the use of the oral route, maintenance of adequate levels and completion of the full course of therapy are not as reliable as with injected penicillin.

Streptococcal infections may also be effectively treated with the broad-spectrum antibiotics. These drugs are equally effective in controlling symptoms and in preventing the occurrence of suppurative complications. Although the advantage of oral administration has made them a popular form of medication, they are not as effective as parenteral penicillin in the eradication of a group A organism.[7] Since penicillin eradicates group A streptococci from the nasopharynx faster and more completely, the use of broad-spectrum antibiotics should be limited to the treatment of streptococcal infections in patients sensitive to penicillin.

PREVENTION OF RHEUMATIC FEVER AND GLOMERULONEPHRITIS

Rheumatic fever and glomerulonephritis are intimately related to streptococcal infections. Careful clinical and bacteriological investigation will almost invariably show that the onset of either of these illnesses follows group A streptococcal infection within a relatively well defined time interval. For this reason these syndromes have come to be known as the late sequelae of streptococcal infection.

Extensive investigation has been centered on the role of streptococci in the development of these late, nonsuppurative sequelae. Group A streptococci produce a variety of enzymatic components and at least three toxins—streptolysin O, streptolysin S and erythrogenic toxin; none of these substances has been shown to have a direct rheumatogenic or nephritogenic effect. Streptococci also contain a number of antigenic components. In patients convalescing from streptococcal infections varying amounts of antibody develop against many of these antigens; though this finding has served to further substantiate the existence of the antecedent streptococcal infection, no features of the antibody response have furnished a clue to the pathogenesis of rheumatic fever and glomerulonephritis.

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PREVENTION OF RHEUMATIC FEVER AND GLOMERULONEPHRITIS

Rheumatic fever and glomerulonephritis are intimately related to streptococcal infections. Careful clinical and bacteriological investigation will almost invariably show that the onset of either of these illnesses follows group A streptococcal infection within a relatively well defined time interval. For this reason these syndromes have come to be known as the late sequelae of streptococcal infection.

Extensive investigation has been centered on the role of streptococci in the development of these late, nonsuppurative sequelae. Group A streptococci produce a variety of enzymatic components and at least three toxins—streptolysin O, streptolysin S and erythrogenic toxin; none of these substances has been shown to have a direct rheumatogenic or nephritogenic effect. Streptococci also contain a number of antigenic components. In patients convalescing from streptococcal infections varying amounts of antibody develop against many of these antigens; though this finding has served to further substantiate the existence of the antecedent streptococcal infection, no features of the antibody response have furnished a clue to the pathogenesis of rheumatic fever and glomerulonephritis.

Features of the host response to streptococcal infection have also been investigated. Such evidence as the tendency of rheumatic fever to occur at different times in the same family has suggested the operation of a hereditary factor, whereas the almost simultaneous development of hemorrhagic nephritis in several persons in a family or school suggested that certain strains of group A streptococci have nephritogenic capacities. Present evidence is insufficient to indicate whether these variations in response are inherited, acquired by previous conditioning or are a result of some peculiarity of the infection or the infecting strain of streptococcus. However, the accumulation of detailed information describing the clinical and epidemiological circumstances associated with the occurrence of rheumatic fever and glomerulonephritis has made it possible to develop practical chemotherapeutic programs for the control of these sequelae. The evidence upon which these programs are based and the recommended prophylactic procedures are summarized in the following sections.

Rheumatic Fever

In children or young adults rheumatic fever has been found to occur in approximately 3 per cent of patients experiencing untreated or inadequately treated infections caused by group A streptococci. It appears to develop after infection of the upper respiratory tract irrespective of the serological type of the infecting organism or the severity of the preceding streptococcal illness. Because the initiating streptococcal infection may be mild, the physician must be alert to detect and to treat these illnesses. It is possible, in view of the occurrence of atypical and asymptomatic infections, that the attack rate of 3 per cent for rheumatic fever would be revised if the streptococcal disease rate could be more accurately determined.

In general, most of the other epidemiological characteristics of rheumatic fever reflect those features of group A streptococcal infections. Initial attacks of rheumatic fever are said to be rare in the infant and infrequent in the preschool child. Since data on the incidence of streptococcal infection in these age groups are difficult to obtain, it is not known whether this reflects the infrequency of streptococcal disease, the smaller possibility of recurrent streptococcal infection or an inability of immature tissues to develop rheumatic inflammation. Unfortunately, the patient who has experienced an attack of rheumatic fever is highly susceptible to a recurrence of this disease.[11] During the first few years following the initial attack, the recurrence rate in patients who are reinfected with group A streptococci may be 10 to 20 times greater than the initial attack rate. Thereafter the recurrence rate declines, but it appears to remain higher than the attack rate of rheumatic

fever in the general population for at least a decade, and perhaps for the duration of life.

Clinically, rheumatic illnesses may vary greatly in severity. Rheumatologists feel that in recent years there has been a marked decrease in the severity of the disease; nevertheless it has been estimated that 50 to 70 per cent of patients with acute rheumatic fever will later have rheumatic heart disease. Since it is almost impossible to predict which patients may subsequently have permanent heart disease, the physician must make every effort to prevent the primary rheumatic attack. Adequate treatment of streptococcal infection prevents the development of clinical rheumatic fever and, therefore, ought to prevent rheumatic heart disease.[11] However, evidence of the prevention of rheumatic valvular heart disease by this method has not yet been obtained; long-term controlled studies are necessary to provide such information.

The main evidence indicating that effective treatment of streptococcal infections will prevent rheumatic fever was obtained from controlled studies in military populations. Typical of the results of this work is the report of one investigation[18] in which treatment of 996 streptococcal infections with various amounts of depot penicillin resulted in a twenty-fold reduction in the incidence of rheumatic fever in comparison with an untreated control group of comparable size. Similar experiences are being accumulated in civilian practice. For example, Breese[2] in 1953, reporting on 1204 treated streptococcal infections in children, found rheumatic fever to occur after therapy of the preceding streptococcal infection in only one instance.

Treatment must be maintained for 10 days so that the group A streptococcus is completely eradicated to obtain maximally effective prevention. Recently it has been demonstrated that penicillin therapy sufficient to eradicate group A streptococci from the nasopharynx appears to be effective in preventing rheumatic fever even when administered late in the course of a streptococcal illness after symptomatic recovery has occurred.[4] Therefore the physician should extend his efforts to prevent rheumatic fever by attempting to diagnose and treat streptococcal infections irrespective of the chronological stage of the illness which the patient presents. The procedures currently recommended by the American Heart Association for the prevention of rheumatic fever by treatment of the preceding streptococcal infection should be used as a guide to therapy (Table 14).

Treatment of streptococcal infections with the broad-spectrum antibiotics is not as effective as parenteral penicillin in eradicating group A streptococci from the nasopharynx and in preventing the development of rheumatic fever. Therefore the use of these drugs in rheumatic fever prophylaxis should be limited to the treatment of infections in persons sensitive to penicillin. Treatment of streptococcal infections with sulfonamides does not result in the elimination of group A streptococci from the tissues of the infected host, and these drugs have no appreciable effect on the subsequent occurrence of rheumatic fever. Sulfona-

mides do prevent the group A streptococcus from parasitizing man, and therefore may be used to prevent the acquisition of streptococci; but they should not be used in therapy once infection has developed, because of their inability to prevent rheumatic fever.

The prevention of streptococcal infections in persons who have had rheumatic fever is of particular importance because of the high risk of recurrence and the accompanying hazard of progressive heart disease in these patients. Since the timely recognition of streptococcal infection

TABLE 14. *Recommended Procedures for the Prevention of Rheumatic Fever**

Treatment of Streptococcal Infections by One of the Following Methods:	
Benzathine penicillin G intramuscularly	
Children:	One injection of 600,000 units
Adults:	One injection of 600,000 to 900,000 units
Procaine penicillin with 2 per cent aluminum monostearate in oil intramuscularly	
Children:	One injection of 300,000 units every 3 days for 3 doses
Adults:	One injection of 600,000 units every 3 days for 3 doses
Oral penicillin	
Children:	250,000 units 3 times a day for 10 days
Adults:	250,000 units units 3 times a day for 10 days
Broad-spectrum antibiotics	
Therapeutic doses for at least 10 days	
Prevention of Streptococcal Infections in Rheumatic Persons:	
Continuous prophylaxis for life by one of the following methods:	
Intramuscular benzathine penicillin G:	1,200,000 units once a month
Sulfadiazine:	0.5 to 1.0 gm. once daily
Oral penicillin:	200,000 to 250,000 units daily†

* As recommended by the American Heart Association.[5] The order of medication is the order preferred by the authors.

† Recent unpublished evidence indicates that it is preferable to give oral penicillin twice daily.

is not always possible, the most effective method at present of avoiding streptococcal infection is to place these patients on continuous chemoprophylaxis. For this purpose 1,200,000 units of long-acting, intramuscular benzathine penicillin monthly or sulfadiazine in doses of 0.5 to 1.0 gm. daily may be used. The choice between these agents depends upon the habits of the patient and the interest of the parents concerned. Some children cannot be relied upon to take oral medication, while others actively dislike the somewhat painful periodic injection of this penicillin preparation. Experience with oral penicillin is limited, and such prophylaxis is more expensive than with the sulfonamides or benzathine penicillin. Further studies with benzathine penicillin may reveal more efficient time-dose schedules and result in a lowering of the incidence of local reactions.

Glomerulonephritis

In contrast to rheumatic fever, glomerulonephritis is a variably occurring sequel of streptococcal infection.[15] Nephritis often appears as a small outbreak in an institution or in several neighboring families. It has also been described as occurring epidemically in outbreaks in which as high as 15 to 20 per cent of patients with streptococcal infection were affected.

The variable attack rate of glomerulonephritis suggested that infection with certain strains of group A streptococci might be more likely to result in this complication. The epidemiological history of this disease since the application of modern streptococcal typing methods has demonstrated this to be an accurate prediction. In the United States glomerulonephritis appears to be associated with infection with group A streptococci of type 12 and less frequently with types 4, 25 and a new strain named Red Lake.[15] A number of carefully observed outbreaks of streptococcal infection caused by other types in which nephritis did not occur provided additional support for the hypothesis that these designated types have particular nephritogenic characteristics. Therefore the serological identification of the infecting strain associated with an outbreak of streptococcal disease can give the physician warning that nephritis may develop.

Careful examination of the urine during the first few days of a streptococcal illness also may provide useful prognostic information. Patients infected with nephritogenic strains who will acquire acute nephritis frequently excrete abnormal numbers of red cells and small amounts of albumin during the febrile stage.[17] These findings disappear with recovery from the acute illness, but return after an interval averaging 10 days from the onset of the original streptococcal illness if frank nephritis develops. Patients who experience primary attacks of acute glomerulonephritis following hemolytic streptococcal infection usually recover and do not show evidence of chronic nephritis at a later date.

In contrast to rheumatic fever, recurrent attacks of acute nephritis are rare. This may be a result of protection given by the formation of type-specific antibody to the nephritogenic infecting type; since there appear to be only a few types associated with nephritis, another infection with a different nephritogenic type is unlikely.[15]

The prevention of primary attacks of acute nephritis in the general population appears to be more difficult than the prevention of rheumatic fever. In the only study that has been reported,[17] early treatment of type 12 streptococcal infections resulted in an incidence of nephritis of 4.5 per cent as compared to an untreated control group in which 11.1 per cent of the patients had acute nephritis. It is possible that streptococcal injury to kidney tissue takes place so early in the course of infection that eradication of the organism with penicillin after typical

symptoms have appeared is not soon enough to prevent the development of the renal inflammatory reaction. Nevertheless, until further evidence is accumulated, prevention of nephritis by the above procedure should be attempted, and particular effort should be made to administer penicillin as early as possible in the course of the streptococcal infection.

The prevention of nephritis by the application of streptococcal prophylaxis in contacts of patients who have already acquired glomerulonephritis may be more effective. In schools or other population groups all persons found by throat culture to harbor hemolytic streptococci who have had contact with patients with nephritis should receive penicillin prophylaxis. Benzathine penicillin is preferable because of the longer duration of protection it provides. Prophylaxis should be continued until new cases of nephritis or new cases of streptococcal infection caused by a nephritogenic strain no longer appear. Because patients with acute nephritis usually recover completely and do not appear to be susceptible to recurrent attacks, long-term prophylaxis against streptococcal infection is not necessary. The only exception would be the rare situation in which such a person might be exposed to a strain with known nephritogenic potential different from the type associated with his original attack of nephritis.

Patients with chronic nephritis, on the other hand, frequently have acute exacerbations following a variety of infections. Since these episodes occur without warning soon after the onset of the precipitating illness and may lead to acute or cumulative renal failure, it would seem advisable to place these patients on continuous prophylaxis using one of the long-term methods suggested in Table 15.

SUMMARY

The diphtheria bacillus and the group A streptococcus are the two bacterial agents usually associated with infection of the nasopharynx. Diphtheria, characterized by extensive membranous exudate, is insidious in onset, but may progress to a serious toxemia. Prompt treatment with antitoxin is necessary to neutralize additional toxin formed and prevent progression of the disease. Penicillin is the agent of choice in the eradication of the diphtheria bacillus.

Streptococcal infection, the most common bacterial disease of the nasopharynx, may occur in several forms. Typical infections, sudden in onset, are characterized by fever, dysphagia, exudative lesions of the tonsils and/or pharynx, and tender, enlarged cervical nodes. Atypical infections may appear as mild nasopharyngitis. They are more frequent in younger children and are often accompanied by a purulent nasal discharge and suppurative complications. Completely asymptomatic

streptococcal infections may be found in all age groups. Laboratory procedures, particularly the total leukocyte count and the throat culture, are valuable aids in confirming clinically apparent streptococcal illnesses and in detecting atypical infections.

Parenteral penicillin is recommended for the treatment of group A streptococcal infections; the tetracyclines are best reserved for the treatment of patients sensitive to penicillin. Therapeutic regimens should provide 10 continuous days' exposure to an antibiotic to ensure eradication of the streptococcus.

Eradication of this organism appears to be essential for the prevention of rheumatic fever and perhaps glomerulonephritis—the nonsuppurative sequels of group A streptococcal disease. Evidence has been accumulated that adequate therapy of streptococcal infections even after their onset will prevent the subsequent development of acute rheumatic fever. Continuous prophylaxis for life with sulfonamides or antibiotics is recommended for the protection of known rheumatic persons from streptococcal disease and the ensuing hazard of recurrent rheumatic fever.

Though the prompt and adequate treatment of streptococcal infection was not as effective in reducing the incidence of acute glomerulonephritis as in preventing the occurrence of rheumatic fever in the one controlled study that has been reported, the results obtained justify its recommendation as a useful preventive measure. In addition, it seems likely that prophylaxis against the acquisition of group A streptococci should prevent the possible occurrence of nephritis in persons exposed to nephritogenic organisms. Patients with chronic nephritis should probably receive continuous prophylaxis to prevent the acute exacerbations that often follow bacterial infections in them.

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SYMPTOMATIC RELIEF OF NASOPHARYNGEAL INFECTIONS IN INFANTS AND CHILDREN

The Use and Misuse of Antibiotics, Nose Drops, Ear Drops, Cough Medications and Antihistaminic Drugs

HARRY C. SHIRKEY, M.D.

Rational therapy depends on precise diagnosis. Precise diagnosis, however, is often difficult in many instances of upper respiratory infections (U.R.I.) of infants and children. Because of the frequency of upper respiratory infections in usual pediatric practice and the difficulty of accurate etiological diagnosis, it follows that rational treatment is a great problem.

DIAGNOSIS AND TREATMENT OF UPPER RESPIRATORY INFECTIONS

Practitioners are often able to diagnose certain specific oropharyngeal disease processes from the history and characteristic findings on physical examination. The typical lesions of primary herpetic stomatitis and Coxsackie virus herpangina stand out as examples. When these and a few other diseases are separated from the many other upper respiratory problems, one is left with the common respiratory diseases, which constitute the greatest number of diseases seen in the cooler months of the year, particularly in the infant and small child.

Little difficulty is encountered in establishing the "U.R.I." diagnosis. The problem comes in attempting to decide which ones will and which will not respond to specific antibiotic or chemotherapeutic drugs. Again, certain entities stand out as those which almost all of us would readily

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Little difficulty is encountered in establishing the "U.R.I." diagnosis. The problem comes in attempting to decide which ones will and which will not respond to specific antibiotic or chemotherapeutic drugs. Again, certain entities stand out as those which almost all of us would readily

treat with such therapy, i.e., those which clinically appear to be streptococcal tonsillitis and pharyngitis, acute otitis media, acute sinusitis, cervical adenitis and pneumonia.

Diagnosis and treatment many times go hand in hand; response to therapy often aids in diagnosis, which otherwise is made by "mitts and wits" most frequently. Therapy is started "on the spot." Laboratory aids are often not freely available and, except for the white blood cell and differential count, may not be helpful at the time therapy is instituted. "The decision as to what treatment to use in these uncomplicated upper respiratory infections and fevers is based on good physical examination, clinical judgment and a W.B.C. if possible . . . Specific treatment of complications at their inception rather than at the beginning of the fever, appears to be the most efficacious management when one is able to obtain the W.B.C."[12]

Chemotherapeutic agents and antibiotics lower the complication rate in patients with an initial white blood cell count over 10,000, but apparently increase the rate with a count below 10,000.[12] Sulfonamides and antibiotics are not effective in the treatment of the common cold or common viral diseases.[12] The common "cold" may be difficult to separate from other upper respiratory infections.

Though certain things are helpful to all of us in pediatric practice, each practitioner develops his own criteria and methods of treatment. Many refer to the "indiscriminate" use of antimicrobial agents, but probably no one feels that his decisions result in such "indiscriminate" use and reserve this term for the "other fellow."

It would seem that, once the decision is made to use such "specific" therapy, the treatment then should follow well delineated rules if available. Also, after having arrived at such therapeutic decision, we need always remember that symptomatic and supportive care are often as important as (often more than) the "specific" treatment.

SYMPTOMATIC AND SUPPORTIVE CARE

Antipyretics; Analgesics

ASPIRIN. Aspirin is one of our most familiar and useful drugs; like fire, it is an excellent servant and a poor master. It is the choice pediatric antipyretic in well regulated dosage. Conversely, it is the leading lethal drug used in pediatric therapy. Deaths from aspirin result not only from accidental ingestion, but also from "therapeutic" administration; they follow not only the mistaken ideas of parents, but also many times the faulty recommendations by physicians. There are many dosage schedules, but a simple rule is to offer ½ grain (30 mg.) per pound of body weight per day. This amount is then divided into four hour aliquots. If continuous therapy is given, the time between doses

may be made longer to evaluate the fever on its return. The great variety of aspirin dosage forms and weight of tablets requires specific directions to prevent overdosage.

Although usually administered orally, it is one of the few drugs clinically effective per rectum. Oral administration is often unsafe, particularly under the age of five years, if whole tablets are used. Cooperation is usually lacking in swallowing tablets, so that either crushed tablets or powder is preferable. The powder may be mixed with household syrups or flavors or even foods, e.g., applesauce.

Rectally administered drugs in general should be instilled into an empty ampulla. Otherwise they may be improperly absorbed or "lost in the mud." A small saline enema is particularly indicated in febrile disease, in which instances the stool may be inspissated. Though the enema is most often omitted prior to rectal therapy, it may offer real help in preventing failure of effect (absorption) by this route. Suppositories of aspirin are available and may be divided to approximate dosage by cutting or breaking. Tablets crushed between spoons may be mixed with usually no more than one ounce of water for a retention enema.

Dehydration and poor urinary output result in a diminution of the excretion of aspirin and allow accumulation within the body.

Other antipyretics can be used, but much less pediatric experience exists for such drugs.

Sponge Bathing. This physical method for the reduction of fever usually requires clear directions by the physician if it is to be adequately carried out in the home. Many nursing procedure books may carry outmoded methods. The body is best exposed entirely, with ventilation to allow evaporation of water and the loss of heat from the body. Gentle friction aids. Though tepid water alone is effective, placebo agents may be added, e.g., "soda." The temperature of the water may be progressively decreased by the addition of ice and alcohol for extreme hyperpyrexia.

Cool enemas may also be necessary. On the other hand, the mere removal of clothing and bed clothes may cause a marked fall in temperature. Prophylactic advice against overclothing or overcovering is a part of treatment if hyperpyrexia is usual to a child with a febrile illness, and it is imperative if the child has previously had febrile convulsions.

Sedation and Anticonvulsants

Sedation may or may not be a necessary part of the supportive regimen, but must be added (as anticonvulsant) for a child with a history of "fever fits." Phenobarbital, because of its longer action, is preferred to the shorter-acting barbiturates.

Nasal Obstruction

One need make only one or two after-midnight calls to a screaming infant to realize the significance of a clear nasal airway for the comfort of the infant and his family. Small infants cannot breathe well through their mouths; they swallow air, and "colicky" symptoms follow. Occasionally the common cold with nasal obstruction must be differentiated from intussusception.

Relief of obstruction may be effected with one or a combination of the following: isotonic saline solution, vasoconstrictors locally applied, suction. The end point of such treatment is a clear airway, not just doing the procedure.

Normal *saline solution* may be made at home with a level teaspoonful of salt to a pint of water. It can easily be made fresh daily. One-fourth to one-half dropperful is dropped into each nostril with the head tilted backward. It should not be forced. Its irrigation properties may allow vasoconstrictors to get to the surface for action when they are used after the saline irrigation. The vasoconstrictor nose drops may have to be repeated in 10 to 15 minutes after the first instillation.

The *vasoconstrictors*, of course, need no preceding saline if the secretions are thin. Also, one cannot always get parents to do all the things which may help, and the doctor must choose those which are of most help. Most vasoconstrictors are used in the same concentration for infants and children as for adults. Failure usually results from "too little"; 3 or 4 drops in each nostril are necessary. If we choose agents with little chance of central stimulation as Neosynephrine[4] and Paradrine,[4] the values of enough in concentration and volume may be appreciated.

One usually depends on the manufacturer for elegance of physical characteristics of the solutions used, but must always be cautious in using any newer products, for infants in particular, because of the possibility of toxicity, which becomes evident only after clinical use.[1]

The hand administering drops to an infant should rest on the infant's head so that if the head moves, the hand (holding the dropper) will move synchronously. The infant's hands may be restrained above the head (thus holding his own head between his arms) when any medication to the nose, ears or eyes is given.

The "family dropper bottle" is to be deplored because of contamination and spread of infection.[10] The bottle, when empty, should be discarded to prevent bacterial and viral contamination and fungal overgrowth in the solution. Quantities of no more than ¼ to ½ ounce should be purchased.

The use of spray bottles and atomizers is generally not good for infants because of variable dosage (excessive) and resultant absorption.[2] Certainly they should not be used with the infant lying down, since toxicity has resulted through such use.

Discontinuance of vasoconstrictor nose drops after long-continued use (two weeks or more) may result in an abatement of the symptoms of a common cold.

Because of the danger of lipoid pneumonia, oily nose drops should never be used.

Suction. Aspiration of thick secretions before the use of saline solution or vasoconstrictor drops offers much toward clearing the airway. The suction force should be regulated near 5 to 10 cm. of negative water pressure if a gauge is part of the system (mechanical). A water suction apparatus is available for home or office use.

Rubber bulb, glass-tipped nasal aspirators are available at drug stores and are valuable in some upper respiratory infections. Sometimes they offer nothing.

Postural drainage is often rewarding. The infant should be placed on the abdomen on a firm surface to allow secretions to drain. The volume of secretions is frequently surprising.

Steam or water droplet vaporizers as used for bronchitis may likewise offer relief in nasopharyngeal discomfort. The happy baby permits a happy home.

Antibacterial Nose Drops

The normal ciliary activity of the mucosal cells prevents adequate contact of antimicrobial agents and thereby reduces their effectiveness by this route. Parenteral administration of antibiotics and the like seems much more rational.[8] Drug sensitization may follow topical administration. Using the same antibiotic topically as well as systemically might give high local concentration to some areas, but ought not to be depended on alone.

Nasal Jellies

This medication form is difficultly given to children. Temporarily, at least, it further occludes the airway.

Gargles

Gargles are not tolerated by small children and are of questionable value.[19]

Lozenges

The bulk of the respiratory infections are seen in the toddler who will not hold lozenges in his mouth. It is probably just as well that he

does not.[8] They are not, of course, a dependable form of therapy for tonsillitis or pharyngitis.

Ear Drops

Ear drops (warmed) may greatly alleviate the pain of otitis media. Simple agents such as olive oil (sweet oil) and glycerin[5] or those with added local anesthetics, though pain-relieving, may change the character of the tympanic membrane and prevent diagnosis. If possible, the drum should be seen before the drops are used.

Myringotomy may be necessary for its therapeutic effect as well as for immediate symptomatic relief. The indication for it is a bulging drum.

Aspirin as an analgesic plus rapidly acting antibiotics often makes ear drops unnecessary.

External otitis may respond to local therapy or may require systemic therapy, depending on the nature of the process.

Cough Therapy

Success of therapy depends somewhat on understanding the cause of the cough. Antitussive measures are many, and, as is usually true of many agents, none excels all others.

The cough may result from upper or lower respiratory pathology or a combination of these. Even so, the supportive measures are often the same: vapor, nose drops, suction, antitussive drugs. Postural drainage of the infant (p. 159) may give a night of sleep for all members of the household (and neighbors). Dripping from the upper respiratory tract to the bed produces no cough. If the secretions fall backward to the nasopharynx and larynx, cough may be frequent.

Steam vapor or water mist may tender the greatest relief in severe coughing. The vapor is best confined to the bed area with sheets pinned securely to three sides of the bed (crib type) plus one over the top. Steam is best led by a long tube or directed into the bed so that an infant or child cannot touch the source. The open "hot plate" is dangerous; patients have suffered severe burns from their use after bedding has caught fire. Vaporizers should turn themselves off when the water content falls. Volatile agents may be used in low concentrations for their placebo effect, but should not saturate the vapor. Volatile oils may slow ciliary action.[7, 19] The latter is effective only if the mucous blanket can be kept from inspissating. Ciliary action may do what coughing might otherwise have to do.

As summarized by Gold,[9] the old division of cough medications into various types of expectorants is not needed or even advantageous. The end point of the nauseating expectorants (e.g., ipecac) is not sharply delineated to liquefying secretions and may either cause nausea and

vomiting or be ineffective. Nausea and refusal of fluid may defeat the effective hydration of the mucous membrane and the normal activity of the cilia.

Drugs should conform in dosage to the dictum, "enough, but not too much." Thus cough medications are offered in "average dose," but tailored by titration to the particular patient's needs.

Time will not be spent here discussing the many proprietary cough syrups. The drug representatives will bring each to your attention. Use will prove or disclaim promises.

A mild extemporaneous syrup may be made at home from lemon juice, sugar and water and may be freely given. This offers safe, often effective "telephone therapy."

For the severe cough morphine has been advocated by clinicians for centuries. Henoch[14] wrote, "When carefully administered . . . [I have] never seen bad results to follow." Paregoric is a time-tested source of morphine. It is often generally available, too, even for "telephone therapy." One need not approach dosage recommended for analgesia, but effect with paregoric may be reached with 0.06 cc. per kilogram of body weight as a single dose, about one tenth of the analgesic dose of morphine.[13] Larger or repeated doses may be given, again by titration of patient and drug.

The calibrated vitamin droppers offer a more accurate measure than the use of counted drops. Thus the 10-kg. (22 pounds) baby would get 0.6 cc. of paregoric per dose. Accurate dosage by drops is impossible, although frequently used. Dolophine as syrup, and other narcotics (codeine), are estimable and familiar to all.

Antihistaminics

One would not discard these drugs in the treatment of nasopharyngeal symptomatic therapy because they are not of proved benefit in the common cold.[3] They may present some measure of relief in patients with chronic allergic disorders with a superimposed common cold.[11] For children the side effects of sedation are many times welcomed as useful properties of these drugs.

To use a few antihistaminics and gain experience in their use has great advantage over using all of them.

Few of these have suggested dosage on a weight basis for children. The dosage of Benadryl[13] and Pyribenzamine[13] is 5 mg. per kilogram per day divided into four to six doses.

SPECIFIC ANTIMICROBIAL THERAPY

After the decision to use one of these agents has been made, further points must likewise be considered, i.e., which agent, which route, dura-

tion of therapy. Reference is made here to the Symposium on Antimicrobial Therapy for details.[15] No real attempt is made here to duplicate this excellent and comprehensive treatise. Tables 18 and 19 from that symposium are particularly useful.[18] Other papers[16, 22] are helpful in consideration of pediatric antimicrobial therapy.

Which Agent to Use, Which Route

In pediatric therapy the advantages and disadvantages of oral versus parenteral therapy differ in many ways from those of adult practice. The child's fear of the "shot" is familiar to all practitioners, but, of course, does not preclude its use. Actually, the need for parenteral administration often goes hand in hand with the choice of antibiotic. The frequency of vomiting with febrile disease may eliminate oral therapy. In many instances it may be started only after initial injection.

Upper respiratory infections are common to infants and toddlers, who are the very ones who repeatedly refuse oral medicines of any kind. On the other hand, in less severe infections, for a child who seldom vomits with his illnesses and whose history is ready acceptance of oral medication, the oral route is obviously the choice one.

All conscientious doctors frequently must consider the cost of medication to some degree in making a choice. These decisions are more pointed when several family members are to be treated at one time. Yet one is faced with the problem of treating infections which in a few hours may be severe, although mild at onset.

Penicillin[20]

Massive penicillin dosage or the use of renal blocking agents seems generally unwarranted in the treatment of the respiratory infections except in their more severe complications.

Oral. Penicillin V will probably replace penicillin G completely for oral therapy because of its acid stability and higher serum levels.[23] Administered orally, penicillin V produces the results that might be expected from parenteral penicillin G.[21] Because of the greater reliability of penicillin V, we may all find less use for the "needle."

Parenteral. In severe or potentially severe infections this is the choice penicillin route.

Dosage. Dosage should follow some pattern of reasonability. The dose frequently given is that contained in 1 cc. of the parenteral preparation or one teaspoonful of the common proprietary preparations. Drop dosage forms (accurately calibrated) are available for infants.

In prescription writing it is better to dilute the proprietary preparations

with Syrup U.S.P. than to depend on giving fractions of teaspoonfuls. This may be psychologically more acceptable to the family in that a larger bottle is dispensed with little increase in cost. Also worthy of thought is the fact that most household teaspoonfuls contain more than 4 cc. Pharmaceutical houses and nurses likewise share varied opinions as to the interpretation of the teaspoonful as either 4 or 5 cc. For accuracy one may order the number of milligrams and the number of cubic centimeters of oral preparation to be given. One wonders how important such accuracy is when one sees the drug on the child's clothes and the bed clothes.

Duration of Therapy. What is said of penicillin may also be considered in connection with the broad-spectrum antibiotics.

Though the criteria for duration of therapy of certain specific infections (streptococcal tonsillitis) are fairly well set down (see the clinic by Dr. Rammelkamp, p. 146), less well defined limits are available for the simple respiratory infections which may be expected to respond.

Large outpatient practice has shown the advisability of not relying on a single injection of procaine penicillin. Procaine penicillin plus benzathine penicillin for rapid and prolonged therapy may be effective by single injection, especially if fortified by oral penicillin or another agent (sulfonamide). Variable results are mentioned by those who administer benzathine penicillin in a single injection. More than two or three successive daily doses of procaine penicillin are often less acceptable to a parent than to his child. Discontinuance of treatment may result from the parents' decision.

Reaction to penicillin in children constitutes a problem, but is of less serious consequence than in adults.

Streptomycin and Dihydrostreptomycin

Little reason exists for the administration of either of these drugs in the usual upper respiratory infection. There is also little excuse for giving penicillin and streptomycin combinations to infants and children. The "single shot" of the combination is especially deplored. The combinations generally available offer far too much streptomycin, for infants in particular, if more than one injection is given daily. Further, the penicillin usually is for delayed absorption, while the streptomycin is rapidly absorbed.

Streptomycin, if used, is best given in aqueous form tailored to the weight of the patient. Its real advantage lies in the ease of injection with little reaction. In the newborn, in whom gram-negative infections rank high, streptomycin may have its place, but with progressively more bacterial resistance to it, its value is falling.

The Tetracyclines

This group of drugs offers oral therapy with good absorption. Valuable for bacterial infections as they are, there are various infections which are not generally considered remediable by the broad-spectrum antibiotics.

Though parenteral preparations are available for use, the oral preparation is the choice for upper respiratory infections. One may initiate therapy with parenteral (intramuscular) administration in the unusual case and follow with oral administration if vomiting is an initial problem.

Great care is necessary to use the upper outer quadrant of the buttocks, particularly in small infants. By avoiding the area of the buttocks where the great vessels and nerves pass, one avoids hematomas, slough, and paralysis of the legs.

Rectal therapy is contraindicated.

Because of the usually short course in these infections, one seldom sees severe moniliasis (oral or otherwise) or staphylococcal enteritis as an important complication, although in newborn infants moniliasis can be a severe problem.

Fewer gastrointestinal side effects are noted with the newer tetracycline than with its older derivatives.

Erythromycin

The spectrum of erythromycin is wider than that of penicillin, but shorter than that of chloramphenicol or the tetracyclines. Erythromycin may be effective against a number of bacteria causing or complicating upper respiratory infections. Its use need not be synonymous with staphylococcal infections, but such use is well recognized.

It is synergistically active with sulfadiazine and may be combined with it. When combined with sulfonamides in an already prepared mixture, the dosage of erythromycin is guided by the sulfonamide content.

Generally, oral therapy is the effective route; however, an initial parenteral dose may be required.

Side effects seem to be minimal.

Novobiocin (Albamycin, Cathomycin)

The latest addition to the group of antibiotics offers another choice in the treatment of bacterial disease. More experience with it in the usual "outpatient" care of respiratory infections is necessary.

At the time of this writing it would seem best to use other therapy if such is indicated. It is comforting to have an antibiotic to turn to

with otherwise resistant bacteria, especially the staphylococcus. Locally, we have seen skin rashes in a number of patients under treatment with novobiocin.

Chloramphenicol

A well accepted and tolerated antibiotic, chloramphenicol has been of great value in many severe pediatric infections complicating or presenting as an upper respiratory infection, e.g., influenzal meningitis, influenzal laryngitis. Because of many references to hemopoietic side effects, this antibiotic is frequently reserved for severe infections and is less frequently used in the treatment of the upper respiratory infection. This fact may be a "blessing in disguise" in that it gives us a generally effective antibiotic for the treatment of severe or as yet not bacteriologically determined infections.

It is effective by a number of routes, but for general respiratory infections the oral route of the palmitate suspension is best. It is well absorbed from the bowel even in fibrocystic disease of the pancreas. The dose of the palmitate may be greater than that of the chloramphenicol base, particularly in severe infections.

Sulfonamides

For infants and children sulfonamides remain most valuable and inexpensive chemotherapy. The functional excellence of the young kidney makes this group of drugs safe and frequently indicated. The great variety of oral preparations make for ease of administration. They may be used alone or in combination with antibiotics. Dehydration is a common pediatric accompaniment of infection, but in spite of this, relatively few difficulties are associated with the use of sulfonamides. There are many well known untoward reactions. The presence of pus limits their use.

Sulfadiazine, the sulfonamide mixtures, sulfisoxazole (Gantrisin) and sulfadimetine (Elkosin) offer a choice in this group. The latter three may be given in higher dose than sulfadiazine.

Triple sulfonamides and sulfadiazine are probably more potent than sulfisoxazole and sulfadimetine and probably offer fewer individual allergic possibilities.[17]

PROPHYLACTIC ANTIMICROBIAL AGENTS

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PROPHYLACTIC ANTIMICROBIAL AGENTS

Certainly many toddlers have recurrent infections during most of the cool months. These infections are associated with "colds" in the family or among acquaintances. It would be ideal if these infections

could be prevented by drugs, but such is not usually the case. Except for the particularly sensitive streptococcus and a few other sensitive organisms, prophylactic therapy is fruitless.

Except for measles prophylaxis, gamma globulin is not indicated in the prophylaxis of respiratory infections.

SUMMARY

None of the antimicrobial agents has an unequivocally favorable effect in the prevention or treatment of the uncomplicated common cold or simple, acute, nonbacterial respiratory disease. The routine use of these agents for the prevention or treatment of common colds does not seem warranted. On the other hand, they may prove highly useful when bacterial complications are present or may be anticipated, or during periods of high prevalence of infection with hemolytic streptococci or other susceptible bacteria.[6]

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ACUTE INFLAMMATORY DISORDERS OF THE LARYNX AND LARYNGOTRACHEAL AREA

EDWARD F. RABE, M.D.

The acute inflammatory disorders of the larynx and the laryngotracheal area have been known to the medical profession for years as "croup." This term has been generally applied to any affection of the larynx and trachea producing difficult and noisy respirations and often a harsh cough. Although such a syndrome can be produced by a foreign body or tumor in the subglottic region, it is most commonly seen in infants and children as the result of infection within the larynx and trachea. This discussion will be concerned with the syndrome defined as *infectious croup*, an inflammatory disease of the upper respiratory tract characterized by inflammation of the rhinopharynx with downward spread of the infection in the respiratory tract leading to variable degrees of stenosis of the laryngeal, laryngotracheal or laryngotracheobronchial air passages. This stenosis is due to edema and is aggravated by membrane formation. The discussion will be based upon material drawn from the recent literature and upon material derived from our own experiences with 68 cases of the disease treated at Geisinger Memorial Hospital and Foss Clinic in the past five and one-half years.

INFECTIOUS CROUP

LOCALIZATION

Infectious croup is a clinical syndrome and as such implies only difficult and noisy respirations often accompanied by a harsh cough, hoarse voice or even aphonia. A precise localization of the site of the infection causing croup can be made by careful examination of the patient and, if need be, by endoscopic visualization of the airway. Thus children

with signs of upper respiratory tract obstruction (inspiratory and/or expiratory stridor, supraclavicular, intercostal and subcostal retraction) and a hoarse voice with brassy cough have mild supraglottic and moderate subglottic swelling and are classified as having laryngitis. Some children may have most of their infection located in the supraglottic area, and thus show only inspiratory stridor and a tremendously swollen and red epiglottis with little or no hoarseness. These patients are also classified as having laryngitis. Patients with either group of symptoms plus loud moist rales or rhonchi apparently originating in the trachea or bronchi are classified as having laryngotracheitis. Patients with a combination of the above symptoms plus patchy areas of fine moist or sibilant rales are classified as having laryngotracheobronchitis, although, strictly speaking, it should be called laryngotracheobronchopneumonitis, indicating that the pathologic process has extended into the bronchi, bronchioles and alveoli.

Such a localization of infectious croup is justified, for both the duration of illness and the mortality increase as the disease spreads down the respiratory tree. Thus in one reported series[20] patients with laryngitis were hospitalized for an average period of 7.3 days and the mortality of these cases was only 1.1 per cent. Patients with laryngotracheobronchitis, on the other hand, were hospitalized for an average period of 17.7 days and the mortality among this group of patients was 18.6 per cent. No consistent correlation existed between the clinical subdivisions of croup and the necessity for surgical intervention.

ETIOLOGY

None of the terms so far used has any specific etiological significance. There are two proved bacterial agents which cause infectious croup, i.e., *Corynebacterium diphtheriae* and *Hemophilus influenzae* type B.[16, 20, 22, 24] When patients with croup due to these agents are grouped according to their clinical signs and symptoms, examples of laryngitis, laryngotracheitis and laryngotracheobronchitis can be found in each etiological category. However, in a series of 347 cases of infectious croup which were studied in detail, only 14.7 per cent (50 cases) of the patients were found to have disease due to either *C. diphtheriae* or *H. influenzae* type B.[20] In the remaining 297 patients a constantly appearing etiological agent was not discovered by detailed bacteriological study of the respiratory tract and blood. These same patients showed a consistent symptom complex, clinical course and living and morbid pathology, thus implying a possible common etiological agent. (Similar consistency was found in the clinical course and pathology of patients with diphtheritic and *H. influenzae* type B croup.) Since a constantly occurring bacteriological agent was not recovered from this

large group of patients with infectious croup, a nonbacterial agent was suggested as the probable cause of the disease in 85 per cent of the cases under study. Although the significance of other potential pathogens which are often present in the respiratory tract (pneumococci, beta hemolytic streptococci, *Hemophilus influenzae* and staphylococci) was apparently not great in this study, other investigators emphasize the importance of secondarily invading bacteria in adding to the sever-

TABLE 15. *Results of Bacteriological Findings in Normal Children and in Patients with the 3 Etiologic Types of Croup*[21]

RHINOPHARYNGEAL CULTURES	NORMAL PATIENTS (1356 Cases)	DIPHTHERITIC CROUP (22 Cases)	H. INFLUENZAE TYPE B CROUP (28 Cases)	"VIRUS" CROUP (297 Cases)
H. influenzae	32.8%	9.0%*	96.4%++	42.2%+++
Beta hemolytic streptococci	10.0%	23.0%	4.0%	8.8%
Pneumococci	33.8%	45.0%	39.0%	52.2%
Green streptococci+	92.0%	**	**	**
Staphylococci	99.1%	**	**	**
C. diphtheriae	—	100.0%	—	
BLOOD CULTURES				
H. influenzae type B	—	—	89.2%	—
Beta hemolytic streptococci	—	—	—	—
Pneumococci	—	13.6%	—	0.4%
C. diphtheriae (virulent)	—	18.2%	—	—

* Untyped or not type B.

+ This term is used because some green pigment-producing streptococci are serologically hemolytic streptococci, and some organisms which are biochemically *Streptococcus viridans* do not produce green pigment.

** Not tabulated.

++ 82.2% (23 cases) had type B. In the remaining 5 cases (17.8%) all had *H. influenzae* type B bacteremia.

+++ 0.6% of cases positive for type B. However, clinical course and pathology indicated organism was not responsible for the disease. Otherwise, remaining cases untyped or not type B.

ity of the disease.[17, 19] Table 15 summarizes the bacteriological findings in various types of infectious croup as well as in noninfected children of the same age.

The recovery of viruses from the respiratory tract of children with infectious croup has been reported by two investigators.[2, 7] In both instances a rise in neutralizing antibody titer against these agents was found in paired serums from the infected children. Comparative studies of the viruses from the two laboratories showed these agents to be similar.* However, the etiological relation between these nonbacterial agents and infectious croup is still to be proved.

Bacteriological studies of patients with infectious croup have shown that cultures of the nose and throat accurately reflect the bacterial flora of the larynx or trachea.[20] This has practical significance because rhinopharyngeal cultures are all that are needed to detect the flora that may

* Personal communication from Drs. A. J. Beale and R. M. Chanock.

be etiologically significant for the disease in the larynx and trachea. Blood cultures also have a definite value in indicating the etiology of *H. influenzae* type B croup. *Hemophilus influenzae* type B, which are encapsulated, highly invasive bacteria difficult to identify in rhinopharyngeal or tracheal cultures, can be found in 90 per cent of blood cultures of patients with *H. influenzae* type B croup.[20] These bacteria are different from the frequently occurring, unencapsulated, nontypable *H. influenzae*, which are common inhabitants of the infected or noninfected rhinopharynx.

A brief statement with respect to the possible role of allergy in croup is needed. In the study of 297 cases of nonbacterial croup there was no higher incidence of allergy in the patients or their families than in the general population.[21] Cases of croup treated with epinephrine were apparently not benefited by this therapy. Thus infectious croup does not appear to have its basis in an allergic constitution.

In summary, infectious croup can be divided into three etiological categories, *C. diphtheriae* croup, *H. influenzae* type B croup, and nonbacterial or "virus" croup. The role of secondarily invading pathogens in nonbacterial croup is difficult to quantitate, but their frequent presence in the respiratory tract of patients with nonbacterial croup is thought to be worthy of serious therapeutic consideration. Cases of laryngitis, laryngotracheitis and laryngotracheobronchitis occur in each etiological category of infectious croup.

PATHOLOGY

The living and morbid pathology of croup due to *C. diphtheriae* has been thoroughly described, so that only points of comparative interest will be mentioned.[9] Endoscopically, a membranous pharyngitis, laryngitis and tracheitis are supportive evidence but not proof of Klebs-Löffler bacillus infection. Microscopically, the membrane is formed from fibrin exuding from a denuded mucous membrane, plus bacteria, leukocytes and monocytes, and is not characteristic for diphtheria. Degeneration of the mucous glands occurs early in the disease and apparently renders the glands incapable of secretion. Later in the disease submucosal abscesses form. The effects of diphtheritic exotoxin upon the adrenals, kidneys, heart, nerves and liver are too well documented to need further description.

Croup due to *H. influenzae* type B presents a characteristic endoscopic picture. The epiglottis is brilliantly red and markedly swollen, usually two to three times its normal size. These same characteristics are often seen in the aryepiglottic folds and occasionally extend as far down as the false cords and laryngeal ventricles. Exudate is occasionally seen on the tonsils, and rarely a true membrane will involve the uvula

and hypopharynx.[22] Microscopically, marked degenerative changes in the submucosal glands of the larynx and trachea plus the formation of numerous small submucosal abscesses are seen early in the disease, i.e., in patients dying within 20 hours of the onset of clinical symptoms. These abscesses lead to minute ulcerations of the surface epithelium of the epiglottis, larynx and trachea. The lungs also show extreme congestion, often with red blood cells appearing in the pulmonary alveoli.

"Virus" croup is characterized endoscopically by mild supraglottic and moderate to marked subglottic edema. Edema involving the laryngeal ventricles and true cords is frequent. Thin secretions cover the mildly inflamed larynx and tracheal mucosa early in the disease. Later, thin crusts form in the subglottic region, or yellow fibrinous crusts in the tracheal area, even in the absence of tracheotomy or prior instrumentation. Microscopically, cases of "virus" croup show from the larynx to the bronchi patchy areas of exudate composed of fibrin, little mucus, round cells and polymorphonuclear leukocytes. There is a variable degree of mucous gland degeneration from area to area, but where the mucous glands show the greatest degree of toxic degeneration a fibrinous exudate is noted on the adjacent mucosa.[21]

CLINICAL COURSE OF VARIOUS ETIOLOGICAL TYPES OF INFECTIOUS CROUP

Croup due to *C. diphtheriae* is rare today in this country since many children have received active immunization against the disease. However, clinicians must not forget the disease, since not only is active immunization not universal, but also laryngeal diphtheria has been reported among children who have been actively immunized against the disease and in whom measurable antitoxin titers were found at the onset of clinical diphtheria.[13]

Croup due to *C. diphtheriae* occurs most commonly in children between the ages of two and seven years. There is no specific seasonal incidence. The membrane can appear primarily in the larynx in an incidence varying from 25 per cent in one series[4] to 66 per cent of the cases in another series.[14] In the remaining cases the membrane begins in the nasopharynx and spreads to the larynx. Diphtheritic croup is usually preceded for about four days by signs and symptoms of an upper respiratory tract infection. Signs of croup, usually with hoarseness, begin slowly and progress for about two days before the increasingly dyspneic child is hospitalized.

Admission examination reveals a moderately ill child with severe croup, a hoarse voice and tender cervical nodes, sometimes of extreme size. Fever is moderate, the admission temperature averaging 38.0° C. Leukocyte counts on admission average 16,600 with 75 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes. Tracheotomy

is necessary in some 30 to 45 per cent of the cases.[13] The course of these children in the hospital is often prolonged by complications, and tracheotomized patients with diphtheritic croup are hospitalized for an average period of 31 days.*

Croup due to *H. influenzae* type B is dramatic, and the speed with which it affects the patient is bewildering to the uninitiated. Like diphtheritic croup, *H. influenzae* type B croup affects primarily the age group from three to seven years, although children as young as four months and as old as 11 years have been reported. Although it occurs most commonly from November to March, it can be seen in any month.[22]

Characteristically, children with croup due to *H. influenzae* have a sudden onset of sore throat with mild symptoms of upper respiratory infection. Within a few hours the symptoms of sore throat progress so that swallowing is difficult, and with this comes audible inspiratory stridor, not accompanied by hoarseness. Symptoms of upper respiratory tract obstruction during inspiration advance rapidly, and within eight hours of the onset of initial symptoms these children need hospitalization.

Admission examination shows a child who looks seriously ill, and the severity of the illness is out of proportion to either the short duration of symptoms or the degree of anoxia. The temperature is high, averaging 39° C. The affected child tends to sit leaning forward in order to relieve his inspiratory obstruction. If he is permitted or made to lie down, the swollen epiglottis falls over the laryngeal orifice, and the child can suffocate. Palpable tender anterior cervical nodes are found in one third of these patients. Inspection of the throat shows edema and injection of the pharynx, occasionally with exudate. When the epiglottis is visible, an immensely swollen, brilliantly red round ball is seen. (Vigorous attempts to depress the tongue and see the epiglottis should not be made, since this maneuver can lead to sudden permanent respiratory arrest.) A leukocyte count is often highly suggestive of the etiology of the disease, for the average white cell count on admission is 24,000 with a polymorphonuclear leukocytosis of 85 per cent. The differential count sometimes shows a polymorphonuclear leukocyte percentage as high as 97 per cent. Blood cultures are usually positive for the infecting organism.[22]

Because of the frequency of marked supraglottic swelling and the rapid course of the disease 50 per cent of these patients need immediate tracheotomy.[22] In this etiological group of infectious croup there is no correlation between the clinical extent of downward spread of the dis-

* This material is based upon previously unreported data from a study of 17 cases of diphtheria occurring in children hospitalized in the Grace-New Haven Community Hospital from 1937 to 1946.

ease and the necessity for surgical intervention. The rapid development of respiratory tract obstruction in these patients often leads to the production of mediastinal emphysema, subcutaneous emphysema or pneumothorax prior to tracheotomy. These complications prolong the hospital course. If these complications are not present, these patients do surprisingly well if proper chemotherapy and adequate intravenous therapy for shock are immediately instituted. Within 24 hours of the onset of treatment the patient improves and the hospital course is short whether or not tracheotomy has been performed. This is in marked contrast to croup due to diphtheria or to nonbacterial agents.

Croup due to nonbacterial agents is the most common etiological form of the disease.[21] It occurs most frequently from October to April, in boys more often than in girls, and most commonly in children under three years of age. Approximately one third of the children with this form of croup have it more than once, but as the child grows older the attacks are less severe. All patients give a history of upper respiratory disease before the onset of croup. These symptoms last for a day or for as long as three weeks. Whether croup begins suddenly in the middle of the night (so-called spasmodic croup) or appears gradually after the initial onset of hoarseness, only close observation can disclose whether the symptoms will abate or progress. If the symptoms of obstruction of the upper respiratory tract progress, they do so gradually over a 24 hour period. Thus the average period of croup before hospitalization is 1.2 days in the nonbacterial form of the disease. The subsequent course is variable and depends upon how far down the respiratory tract the infection spreads.

Admission physical examination of these children shows, in addition to the findings commensurate with the diagnosis of laryngitis, laryngotracheitis or laryngotracheobronchitis, restlessness and apprehension in proportion to the duration and severity of the respiratory tract obstruction. Toxemia such as is noted in *H. influenzae* croup is not seen in this form of the disease.[21] The leukocyte count is only slightly elevated, the mean count being approximately 12,500, the average differential count showing 63 per cent polymorphonuclear leukocytes and 34 per cent lymphocytes. The necessity for tracheotomy correlates well with the degree of downward extension of disease in this etiological form of croup. Thus tracheotomy was performed in 0.6 per cent of cases of laryngitis, 16.3 per cent of cases of laryngotracheitis and 47 per cent of cases of laryngotracheobronchitis in one series.[21] The duration of the hospital course depends also upon the degree of downward extent of the infection and upon the existence of complications of the disease. Tracheotomized forms of nonbacterial croup are often difficult to manage, and the average hospital stay in one series was 25 days.[21]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients with infectious croup depends in part upon the age of the child. Thus children under 18 months of age with marked respiratory tugging and rapid respirations with indrawing of all the soft parts of the chest could have croup. However, absence of clear-cut inspiratory or expiratory stridor or hoarseness plus the presence of numerous tight inspiratory and expiratory sibilant rales through the entire lung field points to infectious bronchiolitis as the disease in question. This same clinical syndrome in the absence of signs of bronchiolitis would suggest salicylism with central nervous system respiratory stimulation as the cause of the rapid, noisy respirations.

Older children are more likely to aspirate foreign bodies and less likely to have infectious bronchiolitis. Sudden onset of croup is not a reliable sign in the diagnosis of tracheal foreign body. Thus if doubt exists as to whether or not a foreign body is present in the respiratory tract together with subglottic edema secondary to the foreign body, x-ray and fluoroscopic examination of the chest is helpful. Although paradoxical aeration of one side of the chest points to unilateral main bronchus obstruction, bilateral paradoxical aeration and paradoxical change in the heart size with respiration points to the main bronchus or the trachea as the site of obstruction.[18] Endoscopy is then needed to decide whether foreign body or laryngotracheitis is present.

COMPLICATIONS

Complications from croup due to *C. diphtheriae* stem from four sources: reactions to specific antiserum; anoxia from uncontrollable spread of the diphtheritic membrane; secondarily invading bacteria causing septicemia or lobar bronchiectasis; and reactions due to the effect of the diphtheria toxin, which include myocarditis, nephritis, hepatitis, neuritis and cutaneous and adrenal hemorrhage.

In croup due to *H. influenzae* type B the outstanding complication is the extreme toxemia and shock which accompany *H. influenzae* bacteremia. Persistent, severe sore throat with occasional nasal regurgitation for a few days early in the course of the disease has been reported. Crusting of the tracheal and bronchial secretions is seen occasionally, and rarely these patients simultaneously have meningitis due to *H. influenzae* type B.[22] These complications are due to the invasiveness of the bacteria.

The other group of complications occurring with *H. influenzae* croup is due to the partial respiratory tract obstruction. This results in various forms of emphysema (pulmonary interstitial emphysema, mediastinal emphysema, pneumothorax or subcutaneous emphysema). In *H. influenzae* croup these symptoms often precede tracheotomy because of the rapid progression of the disease.

Croup due to nonbacterial agents is fearsome because of the occurrence of two severe complications, namely, crusting of the trachea or bronchi and some form of extra-alveolar thoracic air. Crusting is due to a combination of changes in the mucus-secreting glands of the airway and failure to provide adequate moisture in the inhaled air. Clumsy bronchoscopy causing denuding of the mucosa may add further insult to a previous injury.[10] Crusting occurred in 17 per cent of one series of tracheotomized cases of nonbacterial croup, and the mortality among these cases was 50 per cent.[21] Crusting is not produced by tracheotomy, but occurs in severely affected patients who have widespread and marked infection involving the mucus-secreting glands of the larynx, trachea and bronchi. These patients have both marked subglottic edema requiring tracheotomy and pathological mucus-secreting glands the presence of which predisposes to crusting.

Extra-alveolar thoracic air refers to any or all of the following: pulmonary interstitial emphysema (PIE), mediastinal emphysema (ME) and pneumothorax (PT). The incidence of these complications varies, but in one series of tracheotomized cases of nonbacterial croup 33 per cent of the patients had either mediastinal emphysema or pneumothorax, and among these patients 45 per cent died.[21] The genesis of these complications is attributed to two mechanisms which are identified according to the route the entering air follows and are thus known as the intrinsic or extrinsic route.[15, 21] In the intrinsic route the child inhales and exhales against obstruction, the alveoli are progressively distended with air, and the pulmonary vascular bed is compressed. Eventually some alveoli rupture and air drains into the pulmonary perivascular spaces and on into the mediastinum. Air can then rupture into the pleural space or dissect subcutaneously or intraperitoneally. The intrinsic route is responsible for extra-alveolar thoracic air in children with unrelieved partial respiratory tract obstruction either before or after tracheotomy. The extrinsic route is that followed by air which is sucked behind the pretracheal fascia and down to the superior mediastinum.[21] This occurs if tracheotomy is done in the presence of unrelieved (nonbronchoscoped) respiratory tract obstruction. It is, therefore, apparent that extra-alveolar thoracic air is due either to delay in relieving obstruction or to improper tracheotomy.

TREATMENT*

The methods to be described in managing cases of infectious croup are those we have used in the past five and one-half years. During this

* Dr. Francis W. Davison, Chief of the Department of Otolaryngology, collaborated in the preparation of this portion of the discussion. I wish to express my appreciation for his valuable aid.

time 68 cases of croup have been treated, of which seven were tracheotomized. All the patients survived. Among this group there were 26 cases of laryngitis, 35 of laryngotracheitis and seven cases of laryngotracheobronchitis. Sixty-seven cases were classified as nonbacterial in etiology, and one, a case of acute laryngitis with bacteremia, was due to *H. influenzae*. No cases of croup due to *C. diphtheriae* were seen.

Upon admission to the hospital all patients are examined by the pediatrician and the otolaryngologist. After examination, cultures of the nose, throat and blood are made. If doubt exists as to whether or not a foreign body or membranous laryngitis is present, the otolaryngologist may immediately perform endoscopy. After this the child is placed in an atmosphere of 95 per cent humidity provided by cold steam.* Periodic checks of the degree of humidity are made using a membrane hygrometer, since finely nebulized cold steam does not produce an obvious mist even though the humidity may be 92 to 95 per cent. The patient's hydration is carefully maintained. If the child is having marked respiratory difficulty, intravenous infusion is quickly set up, using a sand bag and a number 23, ¾-inch needle. The technique disturbs the patient very little. Fluid and salt requirements are maintained according to the patient's age, size and degree of fever.[5, 6, 26, 27] If the patient is severely ill or in shock, blood transfusion is instituted immediately. If during the postadmission period the patient seems to be unduly apprehensive, intramuscular sodium phenobarbital in a single dose of 6 mg. per kilogram of body weight is given. When needed, this can be repeated at six-hour intervals. We have frequently used this type of sedation, which we feel has been most important in helping to calm patients and evaluate their need for possible surgical therapy.

Chemotherapy is started immediately after hospitalization and the initial work-up. Specific therapy for *C. diphtheriae* croup is either aqueous penicillin or erythromycin and antitoxin;[1] for *H. influenzae* croup, streptomycin and a sulfonamide or chloramphenicol.[25] In nonbacterial croup chemotherapy is given to prevent secondary infection by the usually occurring nasopharyngeal flora (Table 15). On this basis all patients with infectious croup receive aqueous penicillin, 100,000 units intramuscularly every four hours (for patients weighing more than 25 kilograms, 200,000 units every four hours), together with streptomycin, 0.050 gm. per kilogram of body weight per 24 hours in six divided doses (for patients weighing more than 25 kilograms, 1.0 gm. per square meter of body surface per 24 hours), until hospital discharge. Children suspected of having *H. influenzae* croup are given Gantrisin first intravenously in an eight-hour dose of 0.070 gm. per kilogram and as soon

* An air-driven Croupette (Air-Shields, Inc., Hatboro, Pa.) at 8 pounds' pressure is used.

as possible orally in divided doses. The 24 hour oral dose of Gantrisin is 0.2 gm. per kilogram (for patients weighing more than 25 kilograms, 5.0 gm. per square meter of body surface per 24 hours). In a few patients Aureomycin has been used to supplement the intramuscular therapy in an oral dose of 0.020 gm. per kilogram of body weight per 24 hours (for patients weighing more than 25 kilograms, 0.5 gm. per square meter of body surface per 24 hours). We have seen no need to use other antibiotic agents.

On occasion other types of therapy have been used, but not often enough to yield a basis for any conclusions. In three instances steroids were used. Two children received cortisone orally, and one child received hydrocortisone intravenously. Hydrocortisone was given intravenously in a dose of 4 mg. per kilogram per 24 hours at the rate of 10 mg. per hour. Corticotropin has been tried in this syndrome, but without obvious good effect.[28]

Tracheotomy is done on the basis of closely and consecutively observing the patient and noting whether or not the signs and symptoms of severe respiratory tract obstruction are progressing and whether by auscultation there is moderately poor to poor respiratory exchange. The rapidity of respirations, the degree of tiring, the color and the degree of restlessness of the child are all factors to be weighed in watching the progress of these patients. In cases requiring tracheotomy, a 3.5- or 4-mm. bronchoscope is first carefully introduced. Tracheotomy is then performed under local anesthesia. During the procedure care is exerted so as not to skeletonize the trachea or perforate the apical dome of either pleural cavity, measures used to prevent the development of mediastinal emphysema or pneumothorax. After insertion of the tracheal cannula moderately firm packing about the cannula is done with the use of sterile gauze.

Postoperatively the patient is followed closely by the pediatrician and otolaryngologist, and a nurse is in constant attendance. High humidity is constantly maintained about the post-tracheotomized patient. If crusting of the trachea is a problem, 1.0 cc. of Ringer's solution is instilled periodically into the tracheal cannula followed by aspiration with a whistle-tip catheter. This catheter has an adhesive tape collar about it so that the end cannot protrude more than ¼ inch below the tracheal cannula outlet. Deeper introduction leads to loss of tracheal epithelium and increases the likelihood of crusting. Aspiration of large tracheal crusts is done endoscopically by the otolaryngologist through the tracheotomy wound. We have had no occasion to use wetting agents or fibrinolytic enzymes in post-tracheotomy care. There is no consistent opinion as to the necessity or value of these agents.[11, 12]

Endoscopic aspiration of tracheal crusts from the subglottic region without performing tracheotomy was done with benefit in one child

with laryngotracheitis. This procedure obviously requires an experienced endoscopist with a delicate touch, for clumsy instrumentation will increase laryngeal edema and make tracheotomy mandatory.

Pneumothorax and mediastinal emphysema occurred in two of our patients, but in neither instance was it severe enough to need specific therapy. Severe pneumothorax in children is best treated by constant suction drainage.[3] Mediastinal emphysema is difficult to treat with simple needle aspiration, since the air is enclosed in numerous tissue-bounded blebs.[15] Of special interest is the fact that superior mediastinotomy has been used successfully in treating severe mediastinal

TABLE 16. *Summary of Differentiating Points among the 3 Etiological Types of Infectious Croup*

ITEM	DIPHTHERITIC CROUP	H. INFLUENZAE TYPE B CROUP	"VIRUS" CROUP
Season of highest incidence	Any season	Fall, winter, spring	Winter and spring
Age of highest incidence	3–7 years	3–7 years	0–3 years
Pathology, most frequent site	Supraglottic and subglottic	Supraglottic marked, subglottic mild	Subglottic marked, supraglottic mild
Duration of croup before hospitalization	1–2 days	6–12 hours	1–2 days
Physical findings on admission:			
Pharyngeal membrane	Very often	Rare	Never
Cervical adenopathy	Frequent	Often	Infrequent
Presence of shock	Rare	Common	Rare
Typical leukocyte count (P.M.N.)	12–17,000 (75–80%)	22–25,000 (85–95%)	10–15,000 (60–65%)
Presence of septicemia	Rare	Frequent	Rare
Effective therapy	Penicillin or erythromycin and antitoxin	Gantrisin or sulfadiazine and streptomycin or chloramphenicol	Penicillin and streptomycin

emphysema.[8] Since right-sided heart failure occasionally accompanies pulmonary interstitial emphysema, mediastinal emphysema and pneumothorax,[15, 29] we have digitalized intravenously one severely ill patient with atelectasis, bullous emphysema and probable pulmonary interstitial emphysema.

Diphtheritic croup is rare, and we have not treated a case in the last 12 years. We wish, however, to underscore an easily forgotten fact, namely, that if diphtheria is suspected, antitoxin should be given early and in an adequate dose, i.e., immediately and in a total dose of 40,000 units intramuscularly if the patient is not too sick, intravenously if the patient is very sick.[23]

SUMMARY

Infectious croup is a clinical syndrome of noisy, difficult respirations often accompanied by hoarseness. The site of the lesion producing this

syndrome varies in its extent, but the condition can be diagnosed as laryngitis, laryngotracheitis or laryngotracheobronchitis. Etiologically, any anatomical form of infectious croup can be produced by any one of the three following agents: *C. diphtheriae*, *H. influenzae* type B and a nonbacterial agent or agents. The clinical course, pathology and treatment of each etiological form of the disease differ to some degree from the others (Table 16). Therapy of infectious croup includes the use of penicillin or erythromycin and antitoxin for diphtheritic croup, streptomycin and a sulfonamide or chloramphenicol for *H. influenzae* croup, and penicillin and streptomycin prophylactically (against possible secondary bacterial invaders) in nonbacterial croup. Adjunctive measures of value in the therapy of croup of any etiological form include cold steam, properly chosen and properly used sedation, proper and constant hydration, blood transfusions, tracheotomy and tracheal aspiration. Tracheotomy should never be used as a "last resort," but should always be used as a fairly evaluated logical step in the management of severely obstructed patients with infectious croup. The management of a child with infectious croup by a team composed of a pediatrician and an otolaryngologist is a most logical and rewarding method.

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BRONCHIOLITIS

(Acute Asthmatic Bronchitis, Acute Capillary Bronchitis)

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Bronchiolitis is an acute respiratory infection, characterized by generalized obstructive emphysema and respiratory distress. This infection is most common in infants and usually occurs during the winter and spring months.

ETIOLOGY

The etiology of bronchiolitis has not been established, but probably a variety of infectious agents, chiefly viral, are responsible for this disease. In a few sporadic outbreaks *Hemophilus influenzae* has been isolated with regularity from cultures of the nasopharyngeal or tracheobronchial secretions and has been regarded as the cause for the disturbance. In most instances *H. influenzae* infections of the lower respiratory tract are more commonly associated with acute epiglottitis, acute laryngitis (see p. 169), tracheobronchitis or pneumonia. In most clinics, cultures of the nasopharyngeal and tracheobronchial secretions have yielded a variety of microorganisms, and no species has been isolated with regularity. Table 17 summarizes the bacterial species isolated from nasopharyngeal secretions in 41 patients observed during 1953. Of course the recovery of some of these organisms, especially *D. pneumoniae,* from the respiratory tract is not conclusive proof that they are the causative agents. The findings reported in Table 17 are comparable to those noted by others and may be regarded as indicating the types of bacteria likely to cause secondary bacterial complications.

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Other observations support the opinion that bronchiolitis usually is a nonbacterial infection. Leukocytosis, which is common with many bacterial infections, is observed infrequently in patients with bronchiolitis. The administration of antibacterial drugs does not result in rapid improvement as would be anticipated in bacterial infections.

The assumption that bronchiolitis is usually caused by viral agents is supported by several observations in addition to those already noted. Most patients have been exposed to parents or siblings who have acute respiratory infections such as the common cold, acute undifferentiated upper respiratory tract infections, tracheobronchitis and the like. Occasionally the source case is primary atypical pneumonia. In those instances in which the sources have received antibacterial drugs, the course of their infections has not been significantly altered.

TABLE 17. *Bacterial Species Isolated from Nasopharyngeal Secretions*

SPECIES	NUMBER OF ISOLATIONS
D. pneumoniae	15
Micrococcus pyogenes, var. aureus	9
H. influenzae	5
No pathogens	12

Adams[1] has suggested that a virus similar or identical to that which causes distemper in puppies is the responsible agent for some cases of bronchiolitis or viral pneumonitis in infants. Occasional infants, observed in our Clinic, have shown significant rises in cold agglutination titers during the course of their infections. This latter finding suggests that bronchiolitis is sometimes caused by the same agent that produces primary atypical pneumonia in children and adults. It would appear that bronchiolitis can be produced by a variety of viral agents in addition to those mentioned.

CLINICAL MANIFESTATIONS

Regardless of the etiology, bronchiolitis presents a fairly typical clinical pattern. Bronchiolitis is observed chiefly in infants. The age range of 41 patients is summarized in Table 18. In this group over half the cases were noted in infants up to six months of age and three quarters of the cases in infants up to one year of age. Only two patients older than two years of age were in this group; the oldest patient was four years old. The age distribution of patients with bronchiolitis noted here is similar to that observed by others.

Bronchiolitis is usually preceded by a mild upper respiratory tract infection similar to the common cold. This mild infection usually persists for several days to a week and is characterized by mucoserous nasal

discharge, sneezing, coughing and relatively mild constitutional symptoms. The infant does not appear particularly ill during this time, and physical examination discloses evidence of inflammatory changes in the upper respiratory tract. Examination of the chest usually reveals the presence of coarse rhonchi produced by the secretions in the nose and throat.

The signs and symptoms of a mild upper respiratory tract infection change abruptly with the onset of pulmonary involvement. Marked respiratory distress, characterized by generalized obstructive emphysema, develops within a few hours. Most infants appear severely and often desperately ill. The respiratory rate increases to 60 or more per minute and occasionally exceeds 100 per minute. Cyanosis commonly develops, and tachycardia is noted. A dry cough is usually present.

TABLE 18. *Age at Onset of Bronchiolitis*

AGE GROUP	NUMBER
0–6 months	21
7–12 months	10
13–24 months	8
Over 24 months	2

The most striking changes are noted in the chest and in the muscular efforts necessary to produce respirations. The chest is obviously overexpanded. The anteroposterior diameter of the chest is markedly increased, so that inspection reveals that these infants have a round instead of an oval chest. All the muscles of respiration are hyperactive. Short inspiratory efforts cause retraction in the suprasternal and substernal areas. Occasionally, intracostal retractions are noted, similar to, but usually not as marked as, those noted with severe obstruction of the larynx. Expiration is prolonged, and the abdominal muscles are extremely active in this phase of respiration.

Percussion of the chest produces a hyperresonant note, and the areas of cardiac and hepatic dullness may be obscured. Occasionally one may not be able to localize the heart by percussion. The increase in resonance over the anterior upper sternum is often striking. Diaphragmatic movement usually cannot be determined, although it is often apparent that the diaphragms are markedly depressed. Emphysema may be so marked that the liver and spleen can be palpated several centimeters below the costal margins.

Auscultation of the chest reveals tachypnea and a striking prolongation of expiration. Air exchange is obviously reduced. Sibilant and sonorous rales and rhonchi may be noted, indistinguishable from those noted with bronchial asthma in older patients. Crepitant rales may be heard, either widely scattered throughout both lungs or localized in a

few areas. Usually the extreme emphysema makes it impossible to localize areas of pneumonia or atelectasis even though these occur frequently.

Inflammatory changes, produced by the antecedent upper respiratory infection, are usually observed in the nose, throat and ears. Cyanosis of the face and lips is usually present. Tachycardia is a constant finding. Many infants show mild but progressive dehydration due to poor intake and an increased loss of water from hyperventilation.

Although most infants with bronchiolitis are severely ill, they usually do not have a significant febrile response. Table 19 summarizes the rectal temperatures noted at the time of admission to the hospital in 41 patients with bronchiolitis.

TABLE 19. *Rectal Temperature at Time of Hospital Admission*

TEMPERATURE	NUMBER OF PATIENTS
102–103°	3
101–101.8°	10
100–100.8°	6
Less than 100°	22

Most patients have little or no fever in the early stages of this infection. The severity of the individual case cannot be correlated with the fever. Moreover, throughout the course of the infection most patients do not have high fever. A rise in temperature which appears during the course of the infection suggests the occurrence of a secondary infection, the most frequent being otitis media.

ROENTGENOGRAPHIC EXAMINATION

Roentgenographic and especially fluoroscopic examinations are helpful in demonstrating the generalized obstructive emphysema produced by bronchiolitis. Fluoroscopy shows that both lungs are hyperaerated, and there is often little or no detectable change in the degree of aeration during the respiratory cycle. The heart and mediastinal structures are in their normal position and do not shift with respirations. The generalized emphysema is especially apparent when the infant is examined in the lateral or oblique position. In normal infants the heart and the structures of the anterior mediastinum are in close apposition to the posterior surface of the sternum. In patients with bronchiolitis, however, the hyperaerated lungs protrude over the heart and mediastinal structures to produce an area of increased aeration adjacent to the posterior surface of the sternum. The diaphragm is markedly depressed, often to the level of the vertebral attachment of the tenth or eleventh rib. Furthermore, the diaphragm is flattened and relatively fixed in its position. The diaphragmatic movements are rapid, but the diaphragm

does not move through its usual excursion. In addition to the changes produced by emphysema, fluoroscopic examination may reveal areas of lobular atelectasis or consolidation.

Roentgenograms confirm the changes noted at fluoroscopic examination. It is advisable to have films exposed during inspiration and expiration to demonstrate the shallow diaphragmatic excursions. If atelectasis or consolidation is present, roentgenograms usually demon-

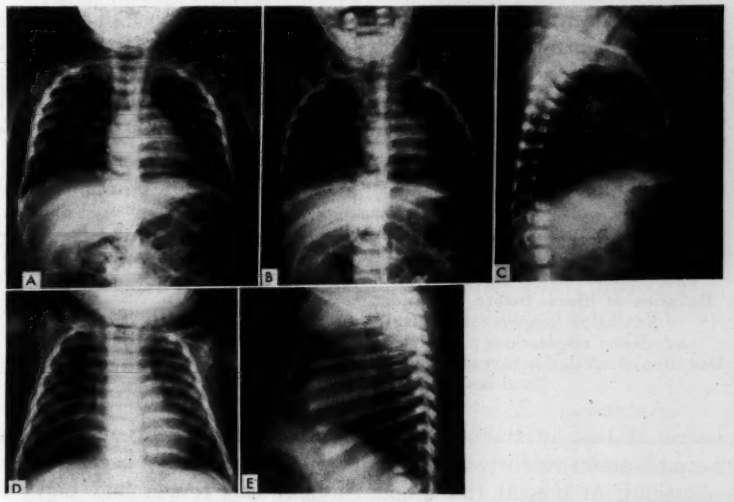

Fig. 32. Bronchiolitis. *A*, *B* and *C*, Case 1. *A*, Roentgenogram taken during inspiration. Note emphysema. *B*, Roentgenogram taken during expiration. Diaphragmatic movement is slight. *C*, Roentgenogram showing emphysema, especially substernally. *D* and *E*, Case 2. *D*, Roentgenogram taken during inspiration, showing severe emphysema. The diaphragm is at the level of the vertebral attachment of the tenth rib. *E*, Roentgenogram showing emphysema, especially substernally.

strate these changes in more detail than does fluoroscopic examination. A generalized increase in peribronchial markings may be noted, suggesting interstitial pneumonitis. The over-all picture is one of severe generalized obstructive emphysema (Fig. 32).

OTHER LABORATORY FINDINGS

Other diagnostic examinations should include cultures of the nasopharyngeal secretions. The usual findings in these cultures have been described. The white blood cell count is usually not elevated, nor is the differential count unusual. The urinalysis is usually normal. Blood cultures are negative, as are tuberculin tests. Mild to moderately severe respiratory acidosis may be noted, and the oxygen saturation of arterial

blood is decreased. If viral diagnostic studies can be performed, appropriate nasopharyngeal washings and serum specimens should be collected. Diagnostic studies, other than the radiological examination, do not aid in the diagnosis of bronchiolitis, but are helpful in excluding other causes of generalized obstructive emphysema.

TREATMENT

The treatment of bronchiolitis is generally supportive and symptomatic. Most patients are benefited by the administration of oxygen which has been adequately humidified. Heavy concentrations of water vapor, produced by mechanical means without heat, likewise seem helpful. Antibacterial agents do not cause dramatic improvement in the

TABLE 20. *Effect of Alevaire on the Course of Acute Bronchiolitis in Infants*

	ALEVAIRE	WATER VAPOR
Number of cases	8	8
Age in months	6.8	6.1
Duration of illness before admission	2 days	1.3 days
Admission temperature (rectal)	101.0°	100.0°
Admission respirations per minute	67	48
Duration of inhalation therapy (hours)	59	40
Total hospital days	7.7	6.4

course of this infection. However, most of the patients who require hospitalization receive such drugs to prevent secondary bacterial complications. At present this hospital usually uses tetracycline, orally or parenterally, because of its action against the common pathogens found in the respiratory tract (see Table 17). Oral feedings should be continued if the infant can nurse easily. The loss of water by hyperventilation must be compensated by increasing the intake of fluids. Many of the infants have too severe respiratory distress to permit oral feedings. Under such circumstances parenteral alimentation is necessary. Since these patients do not have unusual losses of electrolytes, basal needs of sodium and chloride should be met and the remainder of replacement fluids should be free of electrolytes. Oral feedings can usually be resumed in 24 to 48 hours.

Ravenel[5] and Miller[2] recommended the use of wetting agents as aerosols in bronchiolitis. We have been unable to determine that such agents are useful. Significant clinical improvement has not followed the administration of agents such as Alevaire. The results of limited trials with this agent are shown in Table 20. The number of patients is too few to permit an adequate evaluation of this agent, but it is apparent that no striking benefits followed its use. A few patients were examined bronchoscopically before and after the aerosol administration of this

drug. No beneficial effects were noted, and in some infants an increase in the inflammatory changes of the tracheobronchial mucosa followed the administration of the aerosol.

Similar inconclusive results have been observed with the aerosol administration of proteolytic enzymes, including streptokinase-streptodornase, pancreatic dornase and trypsin. The aerosol administration of antibiotic agents likewise does not seem to be beneficial.

A small number of infants with severe bronchiolitis received ACTH or one of the steroid preparations. None of the patients showed rapid or dramatic improvement following the administration of these anti-inflammatory agents.

Bronchodilating agents or antihistaminic drugs also appear to be without benefit.

Tracheotomy is not helpful, since the obstruction is in the small bronchioles and not in the larynx.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes those diseases which produce generalized obstructive emphysema.[3, 4] The most important to consider

TABLE 21. *Differences between Laryngeal Obstruction and Bronchiolitis*

	LARYNGEAL OBSTRUCTION	BRONCHIOLITIS
Respiratory distress	Inspiratory	Inspiratory and expiratory
Stridor	Present	Usually absent
Hoarseness	Present	Usually absent
Chest	Underaerated	Overaerated
Diaphragm	High with maximal excursion	Low with minimal excursion
Respiratory rate	Slightly elevated	Markedly elevated
Retraction	With inspiration	With inspiration, but less marked
Laryngeal obstruction	Present	Absent
Tracheotomy	May be lifesaving	Not helpful

are cystic fibrosis of the pancreas, bronchial asthma, pertussis, pulmonary or miliary tuberculosis and bacterial pneumonia. Other conditions less likely to imitate bronchiolitis include the aspiration of foreign material such as zinc stearate, or irritating gases, endocardial fibroelastosis, various malformations of the heart, anomalies of great vessels, plasma cell pneumonia, the early stage of salicylate poisoning with hyperventilation and respiratory alkalosis, and the like.

Conditions causing unilateral obstructive emphysema are easily distinguished from bronchiolitis, which produces generalized obstructive emphysema.

Obstruction in the region of the larynx produces a clinical pattern which is quite different from that of bronchiolitis. Some of the salient findings in each are presented in Table 21.

COURSE AND PROGNOSIS

Most infants with bronchiolitis have severe respiratory distress for 24 to 72 hours. Oxygen and high humidity are usually necessary during this period, and occasionally infants may require oxygen for as long as one week. The respiratory distress usually subsides gradually, and as it does the infant's general vigor increases. Even the most severely ill patients rarely require hospital care for more than two weeks. Some degree of prolonged expiration may be noted for several weeks after a severe attack of bronchiolitis, but respiration is usually entirely normal by one month after the onset of this disturbance.

Those patients with areas of persistent atelectasis have often been examined bronchoscopically. Usually the only abnormality noted in the tracheobronchial mucosa is generalized inflammation. Occasionally an increase in the secretions is noted; aspiration of such secretions is sometimes followed by expansion of the atelectatic areas. Spontaneous aeration of atelectatic areas usually occurs when bronchoscopic aspiration has not been followed with expansion.

The outlook for eventual, complete recovery is good. We have noted a mortality rate of less than 1 per cent during the past five years. No permanent residua have been noted. Recurrences of bronchiolitis are unusual. Those patients with two or more attacks of generalized obstructive emphysema should be carefully studied for bronchial asthma, even though the latter disturbance is not common in infancy.

Complications occurring during the course of bronchiolitis are usually the result of secondary bacterial infections of the upper respiratory tract. Otitis media is the most common of these. Occasionally pneumothorax may develop in these patients which may be difficult to recognize by physical examination. Roentgenographic examination will be helpful under these circumstances. Aspiration of the pneumothorax is usually necessary.

PATHOLOGY

Since bronchiolitis is rarely fatal, there are only occasional opportunities to study the pathological changes in this disturbance. The gross abnormalities include tremendous generalized emphysema of the lungs with scattered areas of atelectasis and/or consolidation. The larynx, trachea and bronchi usually show hyperemia, but no significant amounts

of exudate or edema. No obstructive lesions are noted in the major bronchi or the branch bronchi.

Histological examination reveals severe thickening of the walls of the small bronchi and bronchioles as a result of lymphocytic infiltrate. This presumably produces a ball-valve obstruction with resultant emphysema. The inflammatory infiltrate extends into the adjoining interalveolar septa. A mild to moderate infiltrate of neutrophils is usually present in the bronchiolar lumens and often in the adjoining alveolar spaces. Severe emphysema is present in addition to patchy areas of atelectasis and bronchopneumonia.

SUMMARY

Bronchiolitis, a pulmonary infection most commonly of viral etiology, produces severe generalized emphysema. This disturbance occurs most frequently in infants and produces a fairly typical clinical pattern. Symptomatic and supportive treatment in association with prophylactic antibacterial agents is usually followed by gradual and complete recovery.

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THE RELATIONSHIP OF CANINE DISTEMPER TO HUMAN RESPIRATORY DISEASE

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HISTORICAL REVIEW

In 1809 Jenner[15] described canine distemper as it occurred in fox hounds and was the first to compare distemper with the infectious fevers of man. Distemper has long been recognized in the canine population in most of the countries of the world, and for many years was considered to be due to bacteria until the studies of Carré[9] in 1905. He first presented evidence of transmission of disease by means of bacteria-free filtrates. *Bacillus bronchisepticus* was found frequently in association with distemper and was considered by many to be the causative agent. However, the Field Distemper Council, which published its reports in 1926, ended the controversy in favor of the original work of Carré. The bronchisepticus, as well as other organisms, was then recognized as a secondary complicating agent. Laidlaw and Dunkin[17] demonstrated six different strains of distemper all of which produced a single type of disease in ferrets, and "these strains cross-immunized against each other." They concluded that distemper can be transmitted by filter-passing material which yields no growth in ordinary culture media and "belongs to the class of filter-passing viruses."

The first report of the transmission of this disease to man was made by Nicollé,[18] who recorded the successful transmission of distemper in an inapparent form to man. In these experiments, man, monkeys and dogs were inoculated simultaneously with a known strain of distemper virus. When the disease was considered at its height in the experimental animals, he successfully transmitted it to normal puppies by means of blood taken from the human host. He interprets this finding as evidence of an inapparent infection in man and states that man can serve as a reservoir of virus for animals, or vice versa. He comments further, that if two species are susceptible to viral infection, and in one it is obvious, in the other subclinical, the disease is older in the latter. He reasons therefore that distemper was an original disease of man. Nicollé's experiments were concerned with adult human beings as sub-

jects, and the complex problems of immunity were probably not wholly considered.

Other observations on the transmission of a respiratory disease from man to dogs were recorded by Bryan[6] in 1928, who was able to transmit an infection from himself to puppies which within seven to 10 days "went down with the typical picture of canine distemper." He reported 11 children in his paper, all of whom presented evidence of a cross-infection between distemper and human respiratory tract infection. Whitney[22] describes "house dog disease" as pharyngolaryngotracheitis which is contracted from human beings suffering from a definite kind of "cold." The systemic form of distemper causes a febrile illness with respiratory symptoms predominant in most susceptible animals. Encephalitis is associated with this disease in about 5 per cent of sick dogs.

Vuori[21] observed a 21 year old patient with transient paralysis of the facial muscles, diplopia and nystagmus, stiff neck, hyperesthesia and exaggerated reflexes which developed three weeks after intimate contact with a dog suffering from distemper. The author suspected that the illness might have been related in some way to canine distemper of the dog.

Clinically, distemper is described as a highly infectious disease having a characteristic biphasic temperature curve. Although many dogs survive the disease, it has a fairly high fatality rate in puppies during epidemics. A condition which causes hardening of the foot pads, called "hard pad disease," appears to be clinically related to canine distemper. When infectious material from dogs with "hard pad disease" is transmitted to ferrets, they die of a disease clinically and pathologically indistinguishable from canine distemper. Recently, Montgomerie* has found evidence of differences between these two strains of virus.

CLINICAL FEATURES

A form of epidemic pulmonary disease was first described in 1941[1, 3] as a primary pneumonitis occurring in prematurely born and young infants. The clinical pattern was uniform in most of the patients and consisted in mild cough and sneezing; in many severe cough, dyspnea, cyanosis and death resulted. A biphasic type of fever was observed in many of the patients. The disease was highly contagious, particularly in infant wards in the institutions where it was first studied. Initially our attention was directed to the most severely ill babies with pneumonitis, and we failed to appreciate the significance of the mild illnesses which occurred in all the other babies at the same time. We now recognize a wide clinical spectrum in this disease similar to that noted in many infectious processes.

* R. F. Montgomerie: Personal communication.

The first epidemic was observed in 1937 before the recognition of atypical or viral pneumonia, and therefore a most thorough bacteriological study was performed. Several types of pneumococci were isolated, but no uniform organism was found, with the exception of three patients with type 27 and four patients with type 23 pneumococci. Two nurses who were considered entirely well were found to be carriers of these two types. No deaths were recorded in patients with specific types of pneumococci. Fresh frozen specimens of lung tissue were sent to Dr. Thomas Francis, Jr., for influenza studies from the patients in the 1937 epidemic. The results of these studies were negative.

The physical findings were minimal and almost entirely confined to the respiratory passages. In the more severely ill, fine rales were heard over the involved areas of the lung, but dullness was rarely elicited. Roentgen studies of many of these patients revealed evidence of overaeration with trapped air and flat diaphragms which is now considered typical of pneumonitis in infants. The clinical course of the severely ill was marked by dyspnea and cyanosis, which appear to occur in attacks. Severe cough was another feature of the illness and at times was almost spasmodic.

PATHOLOGICAL FEATURES

A unique and uniform pathological picture was presented by the necropsy studies. The primary findings were in the lungs and consisted in destructive and proliferative changes in the bronchial pulmonary tree with peribronchial infiltrations of mononuclear cells. In the lining epithelial cells characteristic acidophilic cytoplasmic inclusion bodies were found. These bodies appear to be identical in all respects to those recorded in animals and human beings with known viral infections.

Green and Evans[12] pointed out the significance of vacuolation within the inclusion body seen in distemper. The same characteristic vacuoles were observed in the inclusion bodies from the human cases.

Proliferation to the extent of giant cell formation was found in many of the patients. Giant cell pneumonia was first described by Hecht[13] in 1910 in association with patients with measles. Similar giant cells were found in a few of the patients in the first and second epidemics and are illustrated in Figure 33. In primary pneumonitis of infants and in experimental distemper in ferrets, giant cells are found primarily in the bronchiolar system and appear to be formed from epithelial lining cells. They often contain inclusion bodies, as do the giant cells in measles. Experimentally and clinically, giant cell formation appears to be associated with certain viruses. Morphologically, they form another link in the relation of the present disease in human beings with other viral diseases such as distemper and measles.

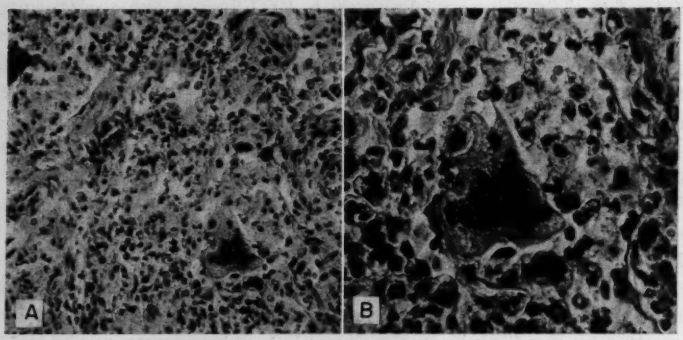

Fig. 33. Photomicrographs from a lung section of a baby with primary pneumonitis, illustrating a low (*A*) and a high power (*B*) magnification of the general pathologic state with characteristic multinucleated giant cells.

The most outstanding and constant clinical-pathological finding in distemper is the presence of cytoplasmic and intranuclear inclusion bodies in lung sections, as well as in urinary sediment cells and in bladder sections. An interstitial pneumonia with peribronchial involvement, made up of infiltrated mononuclear cells, and destruction of lining epithelium were the prominent findings of distempter as recorded by De Monbreun.[10] He describes the inclusion bodies in the lung of dogs as follows:

> In all cases cytoplasmic inclusion bodies were found in both bronchial and alveolar cells. In some bronchi they are especially abundant. They were situated in definite vacuoles and appeared well defined, usually round to oval, sometimes elongated. Vacuolated acidophilic bodies most often lie between the nucleus and the outer margin of the cell, but sometimes at the opposite poles of the cell.

The pathological lesions observed in human premature and full term infants were considered identical with those seen in sections from dogs and ferrets dying of proved distemper. The lining epithelial cells of the respiratory passages contain similar cytoplasmic inclusion bodies and cellular changes. Proliferation with giant cell formation was observed in the human lung sections as well as in those of the animals with distemper. These similarities, as noted in distemper, were further identified with the lesions seen in giant cell pneumonia associated with measles, and a possible biological relationship was postulated by Pinkerton, Smiley and Anderson[19] in 1945. Adams, Imagawa, Yoshimori and Huntington[5] likewise point out the similarities in giant cell pneumonia, in patients with measles and in patients who did not have measles. Experimental material in animals and tissue culture studies have also confirmed the similarities between these diseases and further pointed out that no single viral agent is responsible for giant cell formation. A

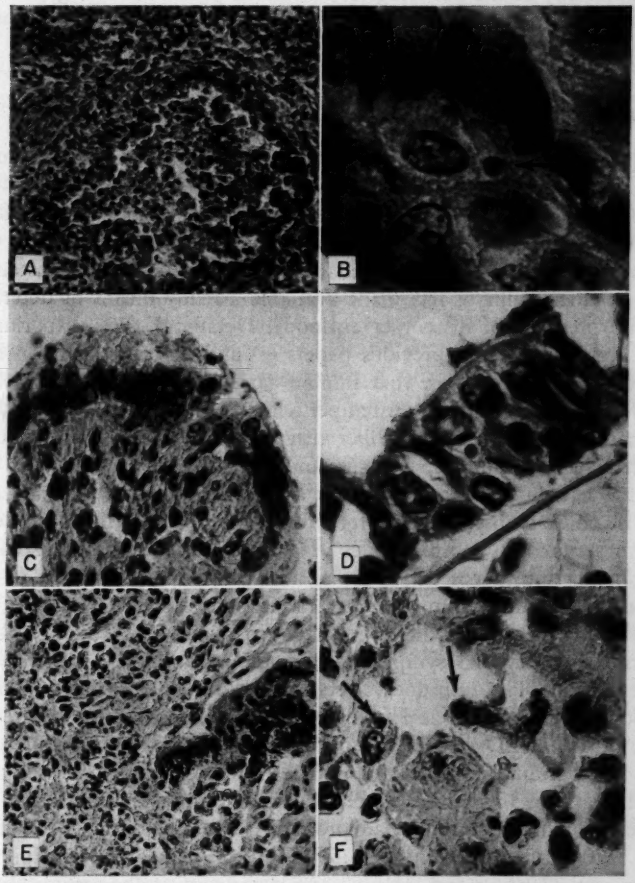

Fig. 34. *A*, Photomicrograph illustrating the pulmonary lesion from an infant with primary pneumonitis in which a small bronchiole demonstrates proliferative changes of the lining epithelium and peribronchiolar infiltration of mononuclear cells. *B*, Photomicrograph of an epithelial cell from the lung of a baby who died of primary pneumonitis, illustrating a cytoplasmic inclusion body with characteristic vacuoles. *C*, Lung section of a ferret which died with experimental distemper, showing proliferative changes. *D*, High power section from the same ferret lung, illustrating a cytoplasmic inclusion body with characteristic halo and small vacuole. *E*, Lung section from an infant who died of measles pneumonia, illustrating a large giant cell with both cytoplasmic and intranuclear inclusion bodies. *F*, Section from the same patient with measles, showing single cytoplasmic inclusion bodies in alveolar cells. Vacuole formation is evident.

brief summary of the pathological features is presented in Figure 34, in which photomicrographs of infant lungs with primary pneumonitis, distemper in ferrets, and measles are arranged for comparison.

IMMUNOLOGICAL STUDIES

Experiments were designed to test human serum and human gamma globulin for distemper-neutralizing substances and to compare the neutralizing properties with hyperimmune distemper antiserum and ferret immune serum. In these studies chick embryos were used along with appropriate controls. The successful cultivation of canine distemper virus in chick embryos has made available a ready means of determining the presence of distemper antibody. Details of these experiments have been recorded in previous papers[2, 14] and will not be given here, but we were able to show that human gamma globulin contained protective substances against distemper virus infections. A study of the serum neutralization of distemper virus in chick embryos was reported by Imagawa, Yoshimori, Wright and Adams,[14] who presented data showing a definite correlation between results of virus neutralization tests in chick embryos and ferret protection tests. Certain samples of human serum and most samples of gamma globulin have distemper-neutralizing substances which are as abundant as those known to exist in specific immune serum. Normal ferrets were shown to have no protective antibodies and died of distemper when challenged. All the ferrets showed typical symptoms of distemper and were dead by the sixteenth day. The immune ferrets, on the other hand, demonstrated antibody levels as high as 1:640, and all these animals survived a challenge of 100 MLD of ferret distemper virus. A few samples of serum from adult human beings have also shown protective titers as high as 1:640. Data on 100 tested samples of adult human serum showed that 44 per cent of the serums had protective substances at a titer of less than 1:20. Protective titers of 1:320 dilution or greater were found in 20 per cent of the tested samples, and 9 per cent of the serums showed protective titers at 1:640 dilution. Tests of serum samples from 12 normal premature infants showed some protective substances at 1:20 dilution of serum, but not at 1:40 dilution. The data indicate that the results of neutralization tests using the egg-adapted distemper virus definitely correlate with ferret protection tests.

Karzon[16] reported on studies on a neutralizing antibody against canine distemper virus found in man and showed that the normal newborn has a positive titer which apparently disappears between six and 12 months of age, but that children from two to 15 years have positive titers with increasing frequency. The incidence of positive titers in adult serums was high. His serum dilutions were only 1 to 5, but the fact that

he was unable to find antibodies in several infants between six and 12 months of age would seem to have some significance in this connection. Using the egg-neutralization test which had previously been reported,[2, 7, 14] he was able to confirm a heat-stable neutralizing substance against the canine distemper virus in human serum, and he also found it to be present in high titer in human gamma globulin. He stated that the neutralizing substance is transmitted by way of the placenta quantitatively from the mother to the newborn infant, but is lost by six months and reappears in the population between the second and tenth years of life. It reaches an incidence of almost 100 per cent in adults, according to his reports. The important point is that human serum does appear to have specific antibodies in surprisingly high numbers.

A recent report by Carlström[8] and a scientific exhibit at the VIIIth International Congress of Pediatrics clearly demonstrated substances in children's serums capable of neutralizing canine distemper virus. By using mice in a neutralization test Carlström showed that animals could be completely protected by serums from older children and adults, but that infants under four years of age rarely showed antibodies with the exception of the newly born. A report by Prier, Wright and Kalter[20] demonstrated the detection of complement-fixing antibodies of Carré's virus; with further improvement, this may become a useful procedure for identifying titer rises in human beings suspected of having a human form of this disease.

Because of the finding of inclusion bodies in the urinary tract of ferrets with distemper, a search has been made in human urinary sediment for cytoplasmic inclusion bodies and other pathological changes in the cells. Certain patients with abacteruric cystitis have been found to have large numbers of inclusion bodies in their urinary sediment cells, and in a few experiments with ferrets immunized with these sediment cells the animals were immune to severe challenge by distemper virus.[4] Further studies along this line are progressing in our laboratory.

In the past few months we have been investigating a possible relationship between distemper and measles. The similar pathological findings in these two diseases, consisting in proliferation of cells with giant cell formation, cytoplasmic and intranuclear inclusion bodies which may occur in the same cell or the same host, led us to undertake these studies.

We have been successful in adapting the measles virus (Enders' strain) to HeLa cell tissue culture. In cultures in which the measles virus is propagated and produces a distinct cytopathogenic effect, neutralization by specific canine distemper antiserum has been observed. Ferrets immunized with distemper vaccines develop substances in their serum which are capable of neutralizing the characteristic changes caused by the measles virus. No neutralizing substances have been

found in control animals or in the serum of animals prior to inoculation. The titers developed have been of a relatively low order such as 1:20 and 1:40, but appear to be comparable to the titers shown by Enders and Peebles[11] and by ourselves in convalescent measles serum. These preliminary studies are being continued in our laboratory and as yet do not make it possible to draw any definite conclusions.

SUMMARY

Canine distemper has been known to be caused by a specific virus for over 50 years, but only recently have we come to appreciate its possible relation to human disease. Distemper in susceptible animals is characterized by an acute respiratory infection. The pathological changes are quite distinct in the lung and bladder epithelium, with proliferative changes and giant cell formation.

Immunologically, the relationship to human disease also exists, since specific distemper antibody has been found in human beings. The normal newborn has a titer which disappears in six months and gradually increases in early childhood to high levels in some adults.

Recently a possible relationship to measles has been under study in our laboratories. Distemper and measles have many properties in common: both are primarily respiratory diseases, both may be complicated by encephalitis, the pathological changes are similar, since both cause proliferation of tissue with giant cell formation, and both produce intranuclear and cytoplasmic inclusion bodies. Evidence of cross neutralization in lower titer has been demonstrated in tissue culture and in animals. Further study is required before the exact relationships will become fully understood. The cause of primary pneumonitis in human beings is not yet known.

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INTERSTITIAL PLASMA CELL PNEUMONIA

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Interstitial plasma cell pneumonia is a severe and often fatal disease of premature and full term infants that occurs at the age of one to four months. The first cases were seen at autopsies almost 20 years ago in central Europe.[4, 11, 23, 24, 27] Since that time many cases have been diagnosed clinically and post mortem in most European countries, and in recent years case reports have been published in the United States and South America.[5, 20, 30]

INCIDENCE

Exact figures of the incidence of this disease cannot be given, since it cannot be assumed that all reports have been published. On the basis of published reports it is probable that there have been more than 2000 cases. In Europe the incidence of interstitial plasma cell pneumonia differs from country to country. In Switzerland, for example, more than 700 cases have been diagnosed,[9] in Czecho-Slovakia more than 300 cases,[17] in Finland more than 200, but in Denmark and Sweden only a few cases.[7, 12] This uneven incidence is not or not alone dependent on how long ago the first cases were seen in the country in question. One has the impression that the disease first existed in a fairly small area of central Europe (Switzerland, Germany, Austria) and then slowly spread from country to country. To my knowledge the manner in which interstitial plasma cell pneumonia has spread has not been studied.

ETIOLOGY AND EPIDEMIOLOGY

Clinical and epidemiological observations suggest strongly that interstitial plasma cell pneumonia is caused by an infectious agent. The

Fig. 35.

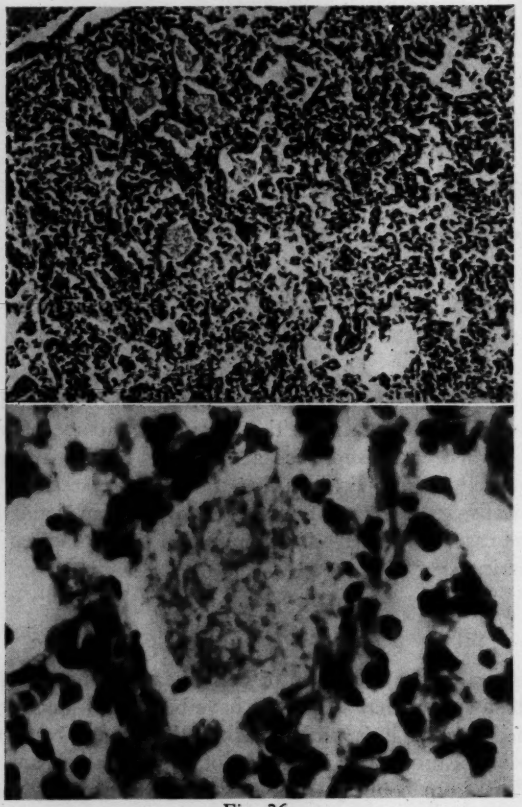

Fig. 36.

Fig. 35. Lungs in interstitial plasma cell pneumonia. The interalveolar septa are thick and contain mononuclear cells. Low power magnification.

Fig. 36. Foamlike matter in the alveolar lumen with *Pneumocystis carini*. High power magnification.

disease is seen mostly in hospitals and institutions—most often in wards of premature infants. The incubation period has been calculated to be 20 to 60 days.[2, 6] The disease seems to be highly contagious. It has not been possible to find any evidence of a bacterial etiology. Virological search for the causative agent has likewise failed.[14, 33] In practically all cases in recent years histological investigations have revealed microorganisms (Fig. 36). Most authorities agree that these organisms are *Pneumocystis carini*, as postulated by Vanek and Jirovec.[31]

Pneumocystis carini is a protozoan found in the lungs of many ani-

mals (rat, mouse, rabbit, dog) as a saprophyte. This protozoan can be stained with the McManus-Hotchkiss method, with Masson's trichrome method, and with Giemsa as well as with Rio-Hortega's silver stain. Some authorities have assumed that the causative organism is a fungus.[10, 18] It has not been possible to produce interstitial plasma cell pneumonia in experimental animals or to prove by any other means that *Pneumocystis carini* is certainly the agent causing interstitial plasma cell pneumonia in infants. The evidence so far is the regular finding of this organism in lung slides at autopsies. While waiting for the results of further investigations it may, however, be reasonably assumed, in the light of our present knowledge, that *Pneumocystis carini* is the agent producing interstitial plasma cell pneumonia.

PATHOLOGICAL ANATOMY

At autopsy the lungs are voluminous, almost filling the thoracic cavity. The color of the lungs is gray or gray-blue. The surface is like a

Fig. 37. White and gray patches and stripes on the cut surface of the kidney.

mosaic caused by the infiltration of interlobular and interalveolar septa. Their consistency is firm. The lungs are airless, and all parts look alike. In some cases interstitial and/or mediastinal emphysema and pneumothorax are seen. There is little or no fluid from the cut surface. The bronchi are empty or contain small amounts of mucus. Microscopically, the alveolar walls are thick, containing plasma cells, lymphocytes and

Fig. 38.

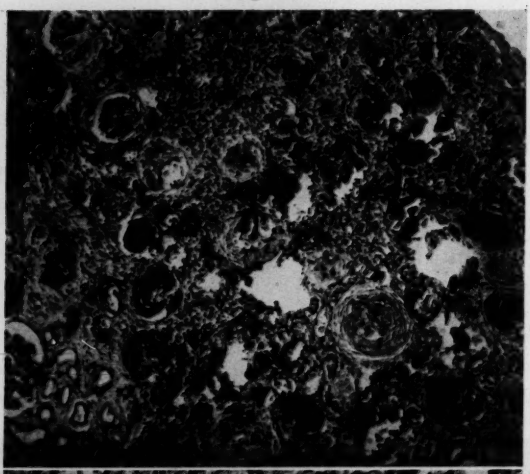

Fig. 39.

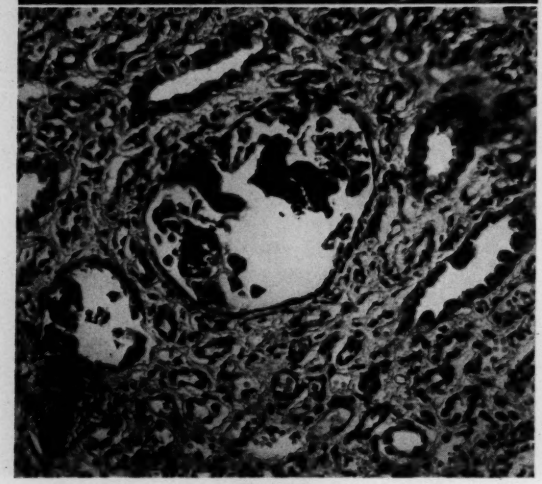

Fig. 38. Scarring of glomeruli with calcium deposits (dark areas) in the tissue. Low power magnification.

Fig. 39. Calcium and desquamation of cells in collecting tubules of the kidney. High power magnification.

fibroblasts. The capillaries are engorged. Alveolar lumens contain foamlike matter in which *Pneumocystitis carini* is seen under high power magnification. Usually there are no leukocytes, though in some cases they are present in alveolar or bronchial lumens. Their presence can be interpreted as a sign of secondary bacterial infection. Hyaline-like membranes are seen in some cases. Small alveolar hemorrhages are sometimes present. The bronchi are empty or contain small amounts of mucus or foamlike matter with *Pneumocystis carini*. The bronchial epithelium is intact.

Findings in other organs are scarce. Many writers mention no abnormal findings in other organs. In some series fairly regular morphological changes in kidneys are described.[1] The kidneys are normal in size and fairly normal in consistency and color. White and gray patches and stripes are seen on the cut surfaces of the kidneys. Microscopically, there are changes in glomeruli, consisting in hyalinization, thickening of the capsule and deposition of calcium. In tubuli desquamation of cells, enlargement of lumens, deposition of calcium, and casts are seen. Some studies indicate pathological findings in the brain, but these findings are not always confirmed.[2, 32] Findings in other organs are less regular and probably of no significance.

CLINICAL SYMPTOMS

The most peculiar characteristic of interstitial plasma cell pneumonia is that it is seen in a narrowly limited age group. The age of patients usually varies between one and four months at the time when the disease is diagnosed. The age at death may vary from two weeks to eight months,[16] but this disease is seldom seen at autopsy after the age of six months. The disease is more common in premature than in full term babies. Full term infants have usually had some debilitating disease before they contract interstitial plasma cell pneumonia, but several reports of this disease in full term infants previously in good condition prove that this is not always so.[16, 29]

The first symptoms may be slight gastrointestinal disturbances, rhinitis, loss of appetite or failure to gain in weight. These symptoms may present themselves even one to two weeks before the appearance of respiratory symptoms. The first symptom noticed may be a slight but progressive increase in the respiratory rate. Tachypnea is the most typical and most important symptom of interstitial plasma cell pneumonia. The respiratory rate increases daily to 80 to 120 per minute. Simultaneously, with the increasing respiratory rate, the dyspnea grows worse.

At the beginning the infant is not critically ill, but in a few days his condition deteriorates. His complexion is pale, with a blueness around the mouth at first, but, as the disease progresses, he becomes pale gray

or gray, and cyanotic, and a shocklike condition develops. He now uses auxiliary respiratory muscles and seemingly has a severe oxygen want. Respiration is abdominal, and there is retraction of the sternum and flanks. On physical examination of the lungs the findings are scarce in contrast to the severe respiratory distress. There is a slight dullness over the dorsal regions at percussion, and the respiratory sounds are less audible than usual. A few rales or none at all are heard. Often nothing abnormal is found. The heart sounds are normal. The temperature is slightly elevated or normal. In the most severe cases the patient lies in the opisthotonos position and seems to be suffocating at every moment. This state persists for days, and the patient either dies with increasing respiratory difficulties or begins to breathe in a less dyspneic way; his color becomes better, the respiratory rate decreases slowly, and the patient recovers within days or weeks. This might be called a typical sequence of events.

Sometimes the symptoms are less marked. The respiratory rate does not increase very much; it may be 60 to 70 per minute. Dyspnea may not be marked, and the course is not of long duration. In these cases the baby is not critically ill. Epidemiological data, together with x-ray studies, may help in making the diagnosis in these cases.

There is not always a correlation between the respiratory rate and the severity of the disease. Often a daily increasing respiratory rate is a sign of worsening of the situation, and a decreasing respiratory rate a sign of a better outlook. In some cases the disease develops at home unrecognized by the parents, and the patient dies at home or during transportation to the hospital. Interstitial plasma cell pneumonia has sometimes been found as the cause of sudden death.[2, 12]

The whole duration of the disease varies very much. In some fatal cases it is seemingly not more than a few hours, but this is not so in patients who present their first symptoms in a hospital with a staff familiar with this disease. Recovery may take weeks or even months.

ROENTGEN FINDINGS

Radiography is the most important diagnostic aid. In the early state of the disease there are densities in the hilar regions or spotlike densities in both lung fields. Later on the densities grow in size and become more marked. In the most severe state of the disease both lung fields are shadowed diffusely and severely. No air-containing area is visible. Interstitial emphysema and/or mediastinal emphysema, as well as pneumothorax, may complicate radiographic study. Radiographic findings may be fairly pronounced with slight clinical symptoms. In incipient cases the similar distribution of densities in various parts of the lungs may make radiographic recognition of the disease difficult. Serial radio-

Fig. 40. Fig. 41.

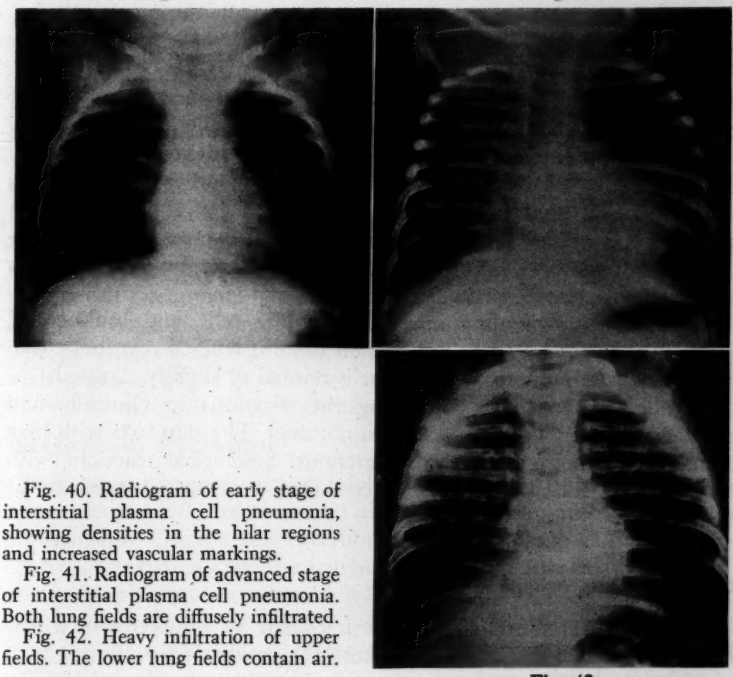

Fig. 42.

Fig. 40. Radiogram of early stage of interstitial plasma cell pneumonia, showing densities in the hilar regions and increased vascular markings.

Fig. 41. Radiogram of advanced stage of interstitial plasma cell pneumonia. Both lung fields are diffusely infiltrated.

Fig. 42. Heavy infiltration of upper fields. The lower lung fields contain air.

grams often prove useful in the diagnosis of suspected cases. Radiographic data can hardly be called conclusive, but, together with clinical symptoms, they confirm the diagnosis, at least in advanced cases. During recovery the radiographic findings do not show the favorable development of the disease as early as do the changes in the respiratory rate and the other clinical symptoms.

LABORATORY FINDINGS

Laboratory findings are not very typical, but there are some which are worth mentioning. There is an increase of white blood cells up to 20,000 per cubic millimeter. In some cases eosinophils are increased up to 10 per cent. Many premature infants are anemic at this age without any disease. This anemia is hardly intensified during interstitial plasma cell pneumonia. On the contrary, in many cases the red blood cell and hemoglobin values are higher than normal. This is not regular, but in several cases the red blood cell count has been more than 5 million per

cubic millimeter and the hemoglobin value 14 gm. The increase of hemoglobin and red blood cells is noted repeatedly during the disease, with a reticulocyte count higher than normal.[1, 2] The sedimentation rate may be 20 to 30 mm. an hour.

No abnormalities have been found in electrophoretic studies of plasma proteins. Particularly in Finland, exceptionally high plasma calcium values have been found in many cases, the highest being 20 mg. per 100 ml.[1, 2] No changes have been found in other minerals. The explanation of this change has not been found yet. It is not—or not alone—due to excessive vitamin D dosage. There is no evidence of parathyroid dysfunction. High plasma calcium and morphological changes in the kidneys may be related.

Small amounts of albumin, red and white cells, and hyaline and granular casts are found in urine when urine is studied repeatedly during the disease. Nonprotein nitrogen is normal or slightly elevated.

Reliable methods for confirming the diagnosis in clinically and roentgenologically suspected cases do not exist. The skin tests with lung extracts have not given specific reactions. Serological reactions with lung extracts as antigen have given better results, but need to be confirmed.[8]

COMPLICATIONS AND SEQUELAE

In many cases the fatal outcome is caused by a superimposed bacterial infection of the lungs.[1, 3] Because the patient is already in a poor condition, it is difficult to estimate whether the worsening of his condition is due to a complicating infection or to the progress of interstitial plasma cell pneumonia. Radiograms help to detect any complicating interstitial, mediastinal and/or subcutaneous emphysema, as well as pneumothorax. These are dangerous complications, but patients have recovered even after extensive subcutaneous emphysema. Some cases of complicating encephalitis have been reported, but it is not known how common this complication is.[32] In most cases the patient either dies or recovers completely, but there are observations indicating that this is not always true. Mental retardation has been found in these infants more often than in the population in general.[13] The high plasma calcium level persists in some cases. Bone changes, together with mental retardation and persisting high plasma calcium, have been observed.[13]

MORTALITY

The case fatality rate is 20 to 50 per cent in most recent series, but because of the absence of reliable diagnostic criteria it is difficult to estimate the reliability of any given statistics. It seems that epidemics

are of different severity at different times, and mortality is accordingly also variable. One is inclined to think that many slight cases remain unnoticed, which suggests that the disease is not so serious as it is usually thought to be. When all exposed infants are watched carefully during an epidemic and x-ray studies are done repeatedly, many cases are diagnosed which probably otherwise would have remained undiagnosed. If, on the other hand, all exposed infants are sent home during an epidemic in a premature infant ward, probably fewer cases are diagnosed than would be if they were kept in the hospital. These are a few of the factors which make it difficult to compare the real incidence and fatality of the disease in various countries and hospitals. When interstitial plasma cell pneumonia has been diagnosed on the basis of typical clinical and radiological findings, the outlook is always at least doubtful. The direction of the development of the disease can never be foretold with certainty.

THERAPY AND PREVENTION

It is generally agreed that an infant with interstitial plasma cell pneumonia needs additional oxygen. This can be given in an oxygen tent or an incubator. Often a concentration of oxygen as high as 60 to 70 per cent is necessary to keep the patients free of cyanosis. It has been supposed that this could produce retrolental fibroplasia,[22] but the evidence is not very convincing. Oxygen mist is probably the most important help for these patients, who live seemingly in continuous danger of suffocation. The concentration of oxygen can be regulated according to the clinical state of the patient, but one should not leave him without oxygen therapy in spite of the possible danger. Caffeine is needed sometimes for short periods. Digitalis has been used to combat possible heart failure. Cortisone together with antibiotics has been tried without any apparent beneficial effect. The feeding of the patient has to be done carefully, avoiding all strain. A permanent nasogastric polyethylene tube can be used in the same way as for premature infants. The necessary fluid and nutritional requirements must be filled, but it is important to avoid overloading of the circulation with intravenous fluids, if it is necessary to give fluid parenterally. Usually the infants are able to take their fluids orally when a nasogastric tube is used. All extra handling of the patient and unnecessary opening of the oxygen tent or incubator are to be avoided. The oxygen concentration is diminished when the patient's respiration becomes easier and he looks better.

There is no specific chemotherapeutic agent against the possible causative organism. Many antibiotics and chemotherapeutics have been tried. Aureomycin and chloramphenicol have given the best results, at least in some series.[3, 28] Probably the effect of these antibiotics is due

to the prevention and treatment of complicating bacterial pneumonia without any effect on the interstitial plasma cell pneumonia itself. High doses have been used (100 to 150 mg. per kg. per day). One group of drugs tried without success were the antimalarial agents.[16, 28] On the basis of the theory that the causative organism is a fungus, antimycotic media have been tried, e.g., Novex (2,2-dioxy-5,5-dichlordifenylsulfid), 1.5 to 6.0 gm. per day,[21] Kavitrat (Nordmarkwerke) (vitamin K_5),[25] Propyl-Butex (Fa.Bush, London).[25] Hormonal therapy with Cyren has given good results.[19] The good results obtained by some authorities with the aforementioned drugs and with some others have not been confirmed by others.[15, 17, 26] It seems that there is as yet no drug effective against the causative organism. The treatment is mostly symptomatic and consists in treatment and/or prevention of complications.

Since interstitial plasma cell pneumonia is a highly contagious disease, it is important to prevent the spread of infection in the ward. Isolation of sick and possibly infected infants is necessary, but in many cases it is not enough to bring a ward epidemic to a standstill. On many occasions it has been necessary to empty the ward completely, though it has happened that when the ward was reopened after cleaning there has been a new epidemic after a few weeks or months. Ultraviolet light has been used with some success to clean the ward. Experience has shown that a ward of premature infants with earlier epidemics has been free of the disease many years—and perhaps permanently when, after cleaning, painstaking isolation technique and continuous application of ultraviolet light have been used in the ward. If sick infants cannot be isolated in single rooms, it is probably best, thinking of the age limitation of the disease, to keep them together with children older than one year.

SUMMARY

There is some evidence that interstitial plasma cell pneumonia is continuously spreading from its original "native country" in central Europe in every direction. This spread does not take place rapidly, but when the disease has once arrived in any country and especially in any premature ward, it is difficult to eradicate it. The disease is usually seen as hospital epidemics, but single cases are also found—and even in infants who have never been in hospital. The clinical symptoms, radiologic data and pulmonary pathological features of interstitial plasma cell pneumonia are fairly well known. Interstitial plasma cell pneumonia is a contagious disease, as shown by clinical experience, but the postulation that *Pneumocystis carini* is the causative organism needs more evidence than is available at present. The mode of transmission is not known. It is not known why the disease is seen only in early

infancy. There has been some decrease in the fatality rate during the 20 years the disease has been known, but it cannot be said how much this change is due to the improved diagnostic methods and how much to the change in the character of the disease or to the vigorous treatment. No really effective method of treatment exists.

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STAPHYLOCOCCAL PNEUMONIA AND EMPYEMA

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Mention of the word "pneumonia" immediately brings to mind the pneumococcus as the causative agent. Other bacterial types are occasionally responsible for the occurrence of pneumonia in infancy and childhood, and it is the purpose of this essay once again to call attention to the role of the *staphylococcus* in this connection. Staphylococcal pulmonary infections present certain interesting and, at times, distinctive features from the pathological, clinical and roentgenographic standpoints. The staphylococcus is at fault in the majority of instances of empyema in modern pediatric practice. The age incidence is maximal in early infancy. There are a number of important points in the medical and surgical management of these cases which deserve emphasis.

Although the existence of staphylococcal lung infections had been known for some time, Reimann in 1933[25] and MacGregor in 1936[24] were the first to point out that these could represent primary infections, unassociated with viral infections of the respiratory tract or septicemic states. MacGregor called attention to the distinctive pathological features, including that of pyopneumothorax. Forbes[13] emphasized the striking age incidence and the influence of age on case mortality, and with others[3, 8] stressed the diagnostic and prognostic features of complicating pyopneumothorax. During the past decade the important role of the staphylococcus in the spectrum of pulmonary infection in infancy has been attested by a number of reports from Australia, Britain, Canada and the United States. The relative increase in the number of such infections is a matter of record.

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PATHOLOGICAL CONSIDERATIONS

In fulminating cases coming to autopsy within a day or two of the onset of symptoms the characteristic finding is that of one or more large and well defined areas of consolidation; frequently there is in addition a serofibrinous pleural effusion, and subpleural hemorrhages are common. Widespread bronchial involvement is unusual. The consolidated areas are intensely hemorrhagic. On microscopic examination of these, evidences of hemorrhage and exudation are present, together with early suppuration and necrosis of the bronchial walls, interlobar septa and perivascular stroma. Clumps of staphylococci are numerous.

Later definite abscesses are to be seen. These are often multiple, though limited to consolidated areas, vary in size and tend to ramify. Clusters may be seen about the bronchioles. The wall of a smaller bronchus may be intimately involved, and the visceral pleura as well. Small bronchopleural fistulas are common, and occasionally wide pleural rupture is seen. Localized or extensive empyema is a relatively frequent finding, and pyopneumothorax far from rare.

The over-all picture, then, is one of fairly well circumscribed intense inflammation leading to early suppuration, abscess formation and a high incidence of pleural involvement.

PATHOGENETIC CONSIDERATIONS

Staphylococcal infection of the lung may represent a *primary* respiratory infection, the organisms gaining entrance via the upper respiratory tract. Less commonly the infection is *hematogenous*, the primary site of the infection being other than the lung. A number of instances of staphylococcal pneumonia secondary to osteomyelitis have been described. The organism may also enter the lung tissue or pleural cavity directly, as a consequence of thoracic operations or trauma to the chest.

A number of predisposing factors have been recognized, among the more important of which are certain *virus* infections and *cystic fibrosis of the pancreas*. Staphylococcal pneumonia may on occasion complicate such virus infections as measles, chickenpox and influenza. Patients suffering from cystic fibrosis of the pancreas exhibit an unusually high incidence of staphylococcal pulmonary infections. Since this disease is regularly accompanied by abnormalities in the mucus-secreting glands of the tracheobronchial tree, recurrent respiratory tract disease is an anticipated complication, but why the staphylococcus should play such a predominant role as the responsible infecting organism is unknown.

An interesting account of an epidemic of hemolytic staphylococcal infection in a newborn nursery was recently described by Feldman and Annunziata.[11] During a three month period 39 such infections occurred. Many were mild; yet four cases of pneumonia (two of them fatal) were

seen. The staphylococci recovered were uniformly resistant to the action of penicillin. It is of the greatest interest to note that, at the time this epidemic took place, a similar staphylococcus was being recovered from purulent skin and subcutaneous lesions present in the nursery personnel and hospital employees, from postoperative wound infections and from the nose and throat of about one third of all the nursery personnel. One recent study[2] indicated that some 90 per cent of newly born infants carried penicillin-resistant staphylococci in the nose at time of discharge from the nursery. It is evident that sources of infection may be widespread within the hospital community, and that when the newborn infant is involved, a few instances of serious infection, including pneumonia, are certain to occur. Incidentally, this problem is also of real concern to those who care for adults.[15, 28]

INCIDENCE

The difficulties encountered by the clinician in making an etiological diagnosis of pneumonia in infancy are well known. Consequently, many of the estimates of relative incidence are based on analyses of empyema cases.

Recently Disney and co-workers[10] of Birmingham, England, made a significant contribution to our knowledge in this connection. They investigated by means of direct lung puncture a series of infants suffering from pneumonia. Of 88 cases of bacterial pneumonia in infants under two years of age, no less than 35 were identified as due to the staphylococcus. Subtracting six cases occurring as a complication of debilitating illness, it would appear that the staphylococcus accounted for approximately one third of the cases of primary bacterial pneumonia.

Since the cases reported by Disney et al. were seen in a hospital, the bias common to all hospital surveys of illness undoubtedly obtains: namely, many of the more easily treated pneumococcal cases represented by the population under study may well have been cared for at home, a common procedure in modern practice. Even though we grant the possibility of this conjecture and conclude that the true relative incidence of staphylococcal pneumonia is somewhat less than this figure, there can be no doubt of the significance of the reported findings. Modern experience at one large general hospital indicates that the staphylococcus is the organism most commonly isolated in cases of bacteremia.[12]

Other data pertinent to this question concern the relative incidence of staphylococcal empyema. A tabulation made by one of us (G.B.F.[13]) for the presulfonamide era indicated that about 10 per cent of all reported cases of empyema in infancy and childhood were due to the staphylococcus. In recent years, presumably because of the salutary effects of antibiotic drugs on pneumococcal and streptococcal infec-

TABLE 22. *Change in Relative Incidence of Staphylococcal Empyema*

ST. LOUIS CHILDREN'S HOSPITAL[13, 14]					CHILDREN'S MEMORIAL, CHICAGO[22]				
Year	Staph.	Pneumo.	Strep.	Staph.	Year	Staph.	Pneumo.	Other	Staph.
1934–6	6	66	7	7.8	1928–32	14	106	48	8.3
1937–42	31	51	14	32	1941–3	12	20	7	31
1943–7	9	11	2	41	1944–5	5	2	2	56

BIRMINGHAM, ENGLAND[7]		EDINBURGH, SCOTLAND[23]	
Year	% Staph.	Year	% Staph.
1935–8	12	Prior to 1929	3
1940–4	29	1947–49	55

tions, this figure has been greatly increased. Adequate treatment has greatly reduced the incidence of pneumococcal and streptococcal empyema, and the staphylococcus by default has been able to assume a leading role. Table 22 indicates the magnitude of such changes in recent years.

THE INFLUENCE OF AGE

The staphylococcus can cause pneumonia and empyema at any age in man. No data are at hand for contrasting adults and children as to the relative frequencies of such infections, but there are clear indications that age is a factor of great importance within the pediatric age group. There can be no doubt that staphylococcal pulmonary infections are far more common in infancy than in later childhood.

As stated earlier, about 10 per cent of all empyema cases reported in children for the preantibiotic era were due to the staphylococcus. When infants less than one year of age were considered, this figure rose to 45 per cent.[13] Figure 43 illustrates the experience of the St. Louis Children's Hospital over a 10 year period. The relative incidence of staphylococcal empyema is seen to be an inverse function of age. For infants under six months of age, 91 per cent of all cases of empyema were due to the staphylococcus, while in the older child the incidence was low. Of the total cases of staphylococcal empyema recorded for this series, 30 per cent were in infants three months of age or less, and 64 per cent one year of age or less. This tendency for the younger age groups to be more frequently afflicted is borne out by a number of recent studies[10, 17, 26, 29] indicating that from 30 to 70 per cent of the patients are three months of age or younger, and 75 to 95 per cent less than one

year. Indeed, the only exception to this trend is the series reported by Blumenthal and Neuhof.[3] Of 40 cases seen by these authors during the period 1930–45, only nine were in infants three months of age or under, and only 11 less than one year of age.

Other forms of staphylococcal infection are not uncommon in early infancy. In a recent analysis[27] of 15 cases of septicemia of the newborn, three were considered to be of staphylococcal origin; and the authors quote the findings of others to be in the range of 16 to 28 per cent. Studies of infants dying suddenly and unexpectedly have revealed a

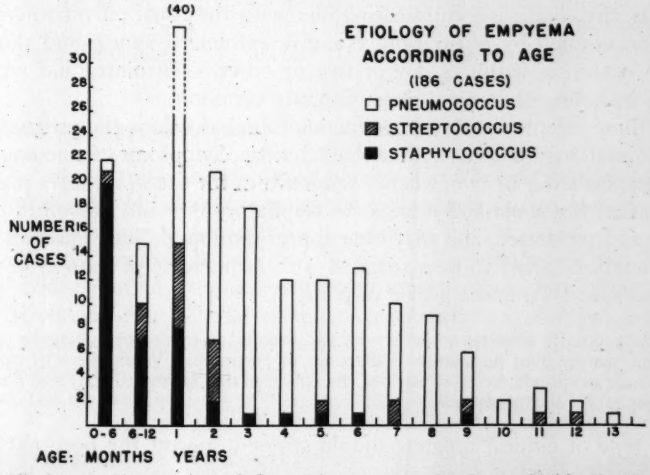


Fig. 43. Age incidence of staphylococcal empyema, St. Louis Children's Hospital Series. (Reproduced from *J. Pediat.*, Vol. 29, by permission of the publishers.)

small, but nevertheless significant, number of instances in which staphylococci were recovered from the blood or from lung tissue.[1]

It is of interest to speculate on possible reasons for the striking age differential noted in cases of staphylococcal pulmonary infection. Concentrations of serum gamma globulin and serum complement are low in early infancy. Levels of circulating staphylococcal antitoxin decrease markedly during the first two to four months of life and remain low throughout the first year.[21] Certainly the lowered resistance of young infants to such diverse infections as tuberculosis and erysipelas and to pathogenic strains of colon bacilli is common knowledge. Information concerning age variations in blood properidin levels will be awaited with interest. Clinicians have long recognized the merits of programs designed to protect the premature, the newborn and the young infant from contact with infective agents.

CLINICAL PICTURE

The presenting symptoms and signs, at least in the early stages, are somewhat variable. In many instances symptoms of pneumonia are preceded by those of an upper respiratory infection from which the expected features of fever, cough and rapid, grunting respirations gradually develop. Occasionally, as mentioned earlier, staphylococcal pneumonia occurs as a complication of a pulmonary virus infection or cystic fibrosis of the pancreas. In some patients the onset of pneumonia is rather insidious, with symptoms and signs in keeping with those of a pneumococcal infection. In others, and most particularly the younger infants, the course is a fulminating one, with the usual pneumonic picture pre-empted by prostration, cyanosis, extreme dyspnea, and shock, death occurring within a day or two of onset. Gastrointestinal symptoms, including abdominal distention, are common.

In those infants in whom pyopneumothorax develops the progress in symptomatology is often rather characteristic. Symptoms of pneumonia progress for a day or two, when a sudden turn for the worse takes place: the infant has a marked increase in respiratory difficulty, becomes cyanotic and prostrated, and may even appear moribund. Such episodes are commonly believed to be associated with an increase of tension in the pleural space. To quote a case in point:

> An infant recently admitted to our service had been taken to a roentgenologist's office for confirmatory films pursuant to a diagnosis of pneumonia. While there he experienced such an episode, which so alarmed the physician that he immediately sent him to the hospital for emergency care.

This type of clinical progress should strongly suggest the possibility of a staphylococcal infection.

In other patients the course is relapsing, with repeated episodes of pneumonic symptoms and signs. Commonly seen in infants suffering from cystic fibrosis of the pancreas, this type of course has reportedly occurred in patients who do not exhibit such predisposing factors.

Despite the occurrence of multiple, small pulmonary abscesses as a common feature of staphylococcal pneumonia, true chronic lung abscess is uncommon.

On examination physical signs of consolidation are frequently elicited. If pleural effusion or empyema is present, characteristically signs can be elicited over the entire involved hemithorax. A flat percussion note and diminution in breath sounds are characteristic; respiratory lag, tracheal and cardiac shift, and fullness of the intercostal spaces complete the picture. However, it should be remembered that breath sounds in young infants may be heard quite well through an area of effusion, and the detection of areas of consolidation is much more difficult than in the older child.

Fever and respiratory distress are common. Severely affected infants appear violently ill—prostrate, cyanotic and even in shock.

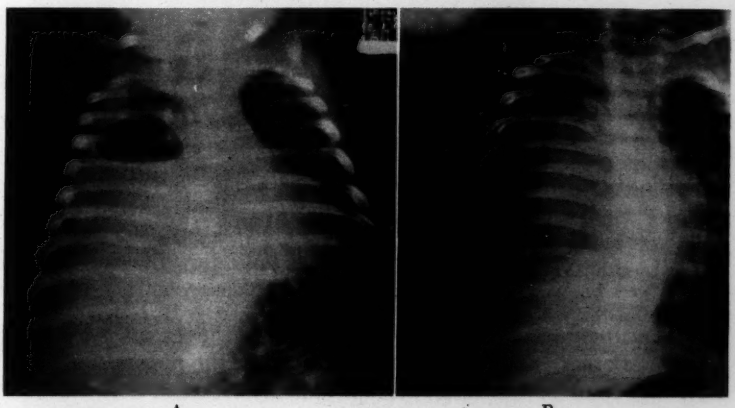
We have seen one patient in whom the only abnormal physical signs (and the roentgenographic findings) were those of pneumothorax due to the presence within the pleural cavity of a large quantity of air and a relatively small amount of pus. In other instances of pyopneumothorax, however, the amount of air present is too small to permit detection by physical diagnostic means.

Polymorphonuclear leukocytosis is characteristic on examination of the peripheral blood. The total leukocyte count may be normal or below normal in the severely ill young infant; nevertheless the differential white blood cell count reveals a marked "shift to the left." A moderate anemia may be seen.

ROENTGENOGRAPHIC PICTURE

The roentgenographic findings are variable from patient to patient and undergo rapid changes during the early stages of the disease. They can be considered under several categories, as follows:

Infiltrative lesions characterize the early stages of the disease. These vary in distribution from segmental and lobar to focal and diffuse. The initial reading may be that of lobar consolidation in one patient and bilateral bronchopneumonia in another. The multiple small abscesses are usually not recognizable as such. There is often nothing to distinguish the picture from other types of bacterial pneumonia.



A B

Fig. 44. Roentgenograms of a severely ill infant with large pyopneumothorax. Upright (*A*) and decubitus (*B*) films demonstrate the pleural nature of the air-fluid level. The child was treated with antibiotics and closed drainage resulting in recovery.

Pleural effusion or empyema. In the young infant the involved hemithorax presents a picture of uniform, homogeneous opacification. Whenever such a picture is seen, pleural involvement is almost a certainty. Shift of the mediastinum is often present. In the older patient pleural involvement may be more localized.

A B

Fig. 45. Roentgenograms showing large tension pneumothorax (A) in a child with almost fatal pulmonary compression secondary to rupture of a large abscess in a case of staphylococcal pneumonia. This was treated by resection of the abscess. Follow-up roentgenogram (B) confirms the satisfactory control of the process.

Fig. 46. Roentgenogram of a 5 year old boy with severe staphylococcal pneumonia leading to such destruction in the basilar segment of the right lower lobe that lobectomy was needed. Note the pneumatoceles in the lateral lung field.

Pyopneumothorax is relatively common. In the experience of ourselves and others, air, as well as fluid, is seen in the pleural space in at least one third of the cases with pleural involvement. The extent of pneumothorax is variable, and is most easily visualized in films taken in the upright position. It may be so extensive as to suggest the diagnosis of spontaneous pneumothorax; the air may be under considerable

tension*; in other instances it is limited, or there may be multiple pockets of air suggestive of multiple abscess formation or cysts. Tension pneumothorax is most apt to be seen in the young infant with profound respiratory distress.

Pulmonary pneumatoceles are commonly seen after the initial stage. They usually present as thin-walled cystlike cavities situated in the pulmonary parenchyma. Occasionally the walls are thick and fluid is present. Characteristically, they produce no symptoms, and persist for weeks or months, gradually diminishing in size. They are rarely seen in other

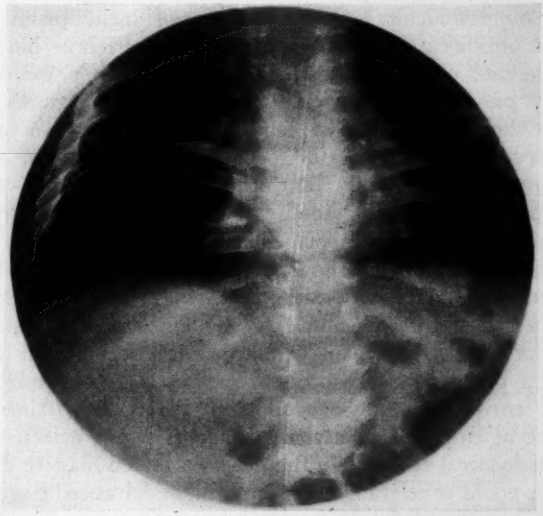


Fig. 47. Close-up view of a typical pneumatocele which disappeared 3 months later.

types of pneumonia and thus are of considerable diagnostic value. Brownrigg[5] notes that pneumatoceles were distinctly less common in those cases undergoing surgical drainage of empyema than in those treated medically.

The pathogenesis is considered to be that of localized peribronchial and bronchial involvement and a subsequent "check-valve" type of mechanism which results in the ballooning out of adjacent tissue.

Campbell et al.[6] discuss the various roentgenographic findings in detail. Representative roentgenograms of cases recently seen on our service are reproduced in Figures 44 through 47.

DIAGNOSIS

This may be difficult in the early stages, when the clinical and roentgenographic picture may resemble that of pneumococcal pneumonia.

* Documentation of the increase in intrapleural pressure is presented in an earlier article.[13]

Representative sputum samples are difficult to obtain, the characteristic salmon-pink sputum* of the adult patient is not seen in infants, and there may be no clue in the patient's symptomatology to suggest the possibility of a staphylococcal etiology.

Recovery of staphylococci from the blood or pleural fluid leaves no doubt, and a pure culture from the nasopharynx is highly suggestive, though one must remember that these organisms can be recovered from the nose in the vast majority of normal persons. The presence of hemolysis in culture and coagulase-positivity are generally taken to be evidences of pathogenicity.† A definitive bacteriological diagnosis is rendered more difficult by the tendency of many practitioners to administer antibiotic drugs early in the course of febrile illness.

The presence of foci of staphylococcal infection elsewhere in the body may provide a helpful clue. An established diagnosis of cystic fibrosis of the pancreas is most helpful, since *Bacillus pyocyaneus* and *Staphylococcus aureus*, singly or together, will account for almost all instances of pneumonia complicating this condition.

The rapid and gratifying response of the usual case of pneumococcal pneumonia to therapy with penicillin is so uniformly seen that the absence of such a response should suggest another etiological agent.

Empyema should be seriously considered in any child with lower respiratory tract disease in whom there is physical and roentgenographic evidence of total involvement of one hemithorax. It is distinctly unusual for a pneumococcal process to present such a picture. The age incidence curve for staphylococcal empyema is so striking that the occurrence of empyema in a young infant is strong evidence in favor of a staphylococcal etiology. In the newborn period massive diaphragmatic hernia could conceivably cause confusion. Advanced stages of lobar emphysema may simulate the tension phenomena of staphylococcal empyema.

Pyopneumothorax is diagnostic; to our knowledge this is seen in no other condition. During convalescence the occurrence of pulmonary pneumatoceles is highly suggestive.

TREATMENT

Medical Treatment

This should be aimed at eradication of the infecting organisms, and involves as its principal parameter the systemic administration of antibiotic drugs. Cultures of the nose and throat, blood and pleural fluid must be obtained prior to therapy.

* One of the authors (G.L.E.) has observed the expectoration of golden-yellow sputum in an adult with overwhelming pneumonia due to *Staphylococcus aureus*.

† Recent data cast some doubt on the validity of this statement. Finland and Jones[12] report a mortality rate of 57 per cent in patients in whom nonhemolytic staphylococci were cultured from the blood.

The sulfonamides are of little value, and staphylococcal antiserum has been abandoned.

Penicillin was found to be a most effective agent when it was first introduced into clinical medicine more than a decade ago. Through the years, however, the frequency of penicillin-resistant strains of staphylococci has been gradually increasing to the point at which it has become common experience to note that well over half of the strains isolated from hospitalized patients are resistant to the action of this drug. Consequently it would seem prudent not to rely solely on this drug for treatment.

The authors prefer to use aqueous preparations of penicillin in large doses in the treatment of any serious infection, including the one under discussion, caused by penicillin-susceptible organisms. Either the intravenous or the intramuscular route may be used. Doses of the order of one to five million units daily are desirable, either as a constant intravenous infusion or intramuscularly in eight divided doses. Local instillations of penicillin into the pleural cavity are recommended by some.

Once the infection is under control, penicillin dosage may be reduced to the range of one-half million units daily, or procaine penicillin preparations (intramuscular route) may be substituted with subsequent reduction in frequency of injections and total dosage.

Of the other antibiotic drugs in common use, *chloramphenicol* and the various *tetracyclines** have been used with success. For oral administration the dose of the former should be 100 mg. per kilogram of body weight daily, and for the latter group of drugs 30 to 40 mg. per kilogram. Preparations for parenteral use are also available (use approximately half the oral dose).

Some of the newer antibiotic drugs, such as *erythromycin, carbomycin* and *novobiocin,* are reported to have potent antistaphylococcal properties, and may prove useful. The nephrotoxic properties of parenterally administered *bacitracin* and *neomycin* are such that these antibiotics should be reserved for desperately ill patients.

Streptomycin is also effective in suppressing growth of staphylococci, but resistance may develop quickly. Doses of 50 mg. per kilogram daily, in two divided doses, may be used. A combination of penicillin and streptomycin is widely used in the treatment of suppurative pulmonary disease, and has proved effective in our experience.

In organizing the treatment program several factors must be considered. Of the drugs listed above, chloramphenicol is the most toxic and penicillin the least toxic; frequency of strain resistance is just the reverse, with the tetracyclines in an intermediate position. Treatment must be started at once if the patient's welfare is not to be compro-

* Tetracycline is marketed under the trade names of "Achromycin," "Panmycin," "Steclin," "Tetracyn," "Polycycline"; chlortetracycline as "Aureomycin" and oxytetracycline as "Terramycin."

mised. It would seem wise to begin treatment by using a combination of two drugs, each in full dosage, continuing until the results of sensitivity tests are known, whereupon changes can be made if necessary. Treatment should be continued until the infection has been completely eradicated, though it should be remembered that pneumatoceles may be visible for several weeks on the roentgenogram.

Other treatment adjuncts are also important: oxygen, measures for the relief of abdominal distention, mild sedatives, antipyretic measures and the like may all be used with benefit. The infant may be relieved somewhat by a semi-upright position or by being placed so that the involved hemithorax is dependent. Transfusions of whole blood may be of help in cases complicated by severe anemia, and parenteral infusions of fluid may be necessary in those patients unable to maintain fluid balance by the oral route. The use of adrenocortical hormones as a supportive measure is not yet a procedure of established merit; indeed, we should like to advise against their routine use in view of reports[12] that they may intensify, or even initiate, serious staphylococcal infections.

Surgical Treatment

Though the primary therapy of staphylococcal pneumonia is medical, there do arise occasions for surgical treatment. These are primarily for dealing with the complications or as an adjunct to medical care. The time for surgical intervention is unpredictable—perhaps early or late in the course of the disease process. Most important is the urgent need for lifesaving drainage in severe, fulminating pleural complications. The anticipated complications of staphylococcal pneumonia which require surgery are empyema, bronchopleural fistula, pleural tension phenomena, fibrothorax and occasional abscess formation.

The most common need for surgery is the occurrence of the pleural complications of the disease. These often develop rapidly and, if untreated, lead to death. The empyema pocket may enlarge, and bronchopleural fistula may occur to perpetuate the empyema or produce tension pneumothorax. Such events lead to overwhelming infection and respiratory embarrassment. Empyema has been treated by aspiration and instillation of antibiotics with varying success. The usual experience, like ours, is that any appreciable collection of pus is more effectively treated by drainage. Repeated aspirations carry some risk and a lessened chance for success.* Early closed drainage is most efficacious. Infrequently it is necessary to do rib resection and resort to an open

* Streptokinase and streptodornase have been advocated as an adjunct to aspiration therapy. Though these do make material easier to aspirate, they carry the risk of opening a bronchopleural fistula. Such temporizing measures are contraindicated in the emergency situations.

procedure. Our preference is for closed suction drainage. This much more frequently than not leads to re-expansion of the lung with obliteration of the pleural space and control of the suppurative process. Intercostal insertion of a large drainage catheter can be readily accomplished under local anesthesia. One must be ready to do this on short notice. It is best done by the physician present rather than waiting for specialized consultation.

When a bronchopleural fistula occurs, drainage should be established immediately, since fistula perpetuates infection. It is through these fistulas that air is valved to produce tension pneumothorax. Suction drainage here serves to relieve the respiratory distress of pulmonary compression, evacuate infected material, and obliterate the pleural space to approximate the fistulous opening and parietal pleura, thus leading to healing.

The findings at autopsy and the few resected specimens indicate that the pleural complications of staphylococcal pneumonia are a gross sign of what is likely to be a small reparable lesion in the lung. Certainly, much useful parenchyma is sacrificed when emergency resections are done in the presence of such a pneumonic process. Resection should be reserved for residual lesions proved to be sources of recurrent trouble. Occasionally a chronic lung abscess or a bronchiectatic area will need excision. We agree with Bloomer et al.[4] in advising against early decortication and corrective surgery.

There are some cases of inadequately or unsuccessfully treated staphylococcal empyema which progress to a crippling fibrothorax. Fortunately, these are uncommon. When they occur, decortication is indicated. We feel that this should not be done as an emergency or unnecessarily early. The same applies to early resection. Much of the change seen in roentgenograms clears over a period of weeks.

In summary, the surgical treatment of the pleural complications of staphylococcal empyema is an emergency procedure. Aspiration and closed drainage should be done at once by the physician caring for the child if thoracic surgical assistance is not readily available. To await such specialized help may court disaster. The less urgent and more complicated problems may well await the thoracic surgeon. Present techniques of anesthesia, surgery and supportive therapy allow one to do many things heretofore unjustifiably hazardous. Now even the extensive and complicated procedures may be done on the very young. As Hertzler et al.[16] recently pointed out, sound surgical principles in the treatment of empyema have not been displaced by antibiotics. Rather, antibiotics have helped to control the suppurative processes in the lung which previously were the cause of death in well treated patients, as shown by Ladd and Swann.[20]

PROGNOSIS

Modern treatment is quite successful. Prior to the antibiotic era, mortality rates ranged from 25 to 70 per cent, whereas recent reports[4, 9, 10, 17, 29] give figures in the range of 0 to 20 per cent. The age of the patient is important, since reported mortality rates through the years have been consistently higher in the first few months of life, with most of the fatalities in infants under one year of age.

A number of complications have been reported, among them myocarditis, pericarditis and brain abscess. Bacteremia is not uncommon, so that metastatic involvement of various organs should be carefully watched for. Occasionally, irreparable damage to the pulmonary parenchyma or chronic empyema occurs, necessitating extensive surgical treatment.

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BRONCHOPULMONARY SUPPURATIVE DISEASE

Differential Diagnosis and Management

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With the discovery and widespread use of antibiotic agents the prevalence of various types of acute and chronic disorders of the lower respiratory tract in children underwent a marked change. With this change we have been faced with an increasingly pressing challenge from a variety of chronic infectious processes in the bronchial tree or pulmonary parenchyma, ranging in intensity from the mild and reversible inflammatory changes of some infectious or allergic bronchitides to such profoundly destructive processes as that associated with fibrocystic disease of the pancreas.

These chronic bronchopulmonary conditions permit arbitrary etiological classification as shown in Table 23. Among these disorders the most urgent diagnostic and therapeutic problems are those presented by the chronic suppurative bronchopulmonary lesion associated with fibrocystic disease of the pancreas, chronic aspiration or foreign body, agammaglobulinemia, certain chronic bacterial, fungal or parasitic infections, and other chronic conditions of unknown cause. It is proposed to review briefly the diagnostic and therapeutic approaches followed in these cases at St. Christopher's Hospital for Children.

DIAGNOSTIC CONSIDERATIONS

History

In sorting out from an etiological standpoint the children presenting chronic bronchopulmonary disorders a carefully taken medical history is of prime importance.

Among the points most helpful in indicating specific disease entities

TABLE 23. *Etiological Classification of Chronic Bronchopulmonary Conditions*

I. Primarily infectious, due to pathogenic microorganisms
  A. Bacterial
  B. Fungal
  C. Parasitic
II. Primarily due to deficient mechanisms of defense against infection
  A. Agammaglobulinemia
III. Primarily obstruction, secondarily infected
  A. Aspiration of food or foreign body
  B. Extrinsic bronchial obstruction from lymph nodes or tumor
  C. Fibrocystic disease of the pancreas (separate category with V or II)
IV. Primarily reactive, secondarily obstructive or infected
  A. Allergic bronchitis
V. Primarily anatomical
  A. Due to developmental defects such as anomalies of trachea or tracheobronchial tree, of chest wall or thoracic spine, heart or esophagus
VI. Of unknown etiology
  A. Idiopathic chronic bronchitis or bronchiectasis, possibly a sequel of such prior infections as pertussis, measles or acute bacterial pneumonia

are age, abruptness of onset of symptoms, their relation to feeding and other activities and to time and place, presence of gastrointestinal abnormalities and nutritional disorders, presence of infection in other systems, and the response to therapeutic measures previously tried. It is often not possible from the history alone to establish a most probable diagnosis, and it is worth remembering that patients with fibrocystic disease of the pancreas may have spasmodic coughing spells and wheezing as the only clinical manifestations. A history of repeated attacks of bronchiolitis sometimes is the first suggestion of fibrocystic disease of the pancreas.

In addition, it will often be profitable to explore the occurrence and exact clinical nature of similar difficulties in siblings and other members of the family. Not uncommonly the siblings of a child with fibrocystic disease of the pancreas had a fatal illness of similar clinical nature, or a child with suspected allergic symptoms has relatives with more clearly delineated allergic difficulty. As Oswald et al.[9] have shown in their review of 1000 adults with chronic productive cough, even when precise diagnostic labels are not available, a high incidence of bronchitis in relatives may indicate a hereditary disposition to pulmonary disorder.

Physical Examination

Special attention should be placed on the respiratory activity of the patient, presence or absence of cyanosis, presence and nature of cough or sputum, nutritional status, clubbing of fingers, abnormalities of the shape of the thoracic cage, and findings on percussion and auscultation of heart and lungs.

Roentgenological Examination

This part of the examination is essential in establishing the extent of pulmonary infiltration or other changes, and should always include both posteroanterior and lateral films, as well as fluoroscopic examination. The latter should demonstrate, in addition to parenchymal lesions, the motions of the diaphragm and other thoracic structures in relation to phrases of respiration.

Bronchography is essential in the accurate appraisal of portions of lung suspected of bronchiectasis, and should ordinarily include the examination of all lobes.

Bronchoscopy

Bronchoscopy should be carried out in almost all cases of chronic bronchopulmonary disease of obscure origin for the direct visualization of larger air passages, and for the recovery of exudate or other material for smear, or for bacteriological or histological examinations, as well as from time to time for the recovery of a foreign body.

Skin Tests

Skin tests may be helpful. They include the tuberculin test and other tests for bacterial or fungal sensitivity, using antigens prepared from *Blastomyces dermatitidis, Coccidioides immitis* and *Histoplasma capsulatum.* As in a positive tuberculin test, a positive reaction to coccidioidin or histoplasmin indicates present or past infection with the respective fungal agent. Blastomycosis, however, does not so regularly induce skin reactivity; a negative skin test should be accompanied or immediately followed by examination of serum for complement-fixing antibodies if the illness is strongly suspected.

Skin testing with potential allergens may also be of help from time to time, either in pointing to specific offenders in the allergic child or, more generally, in indicating, through the demonstration of typical allergic skin reactivity to common allergens, the possible or probable allergic nature of a child's difficulty. *Negative skin reactivity does not,* however, *exclude the possibility of intrinsic or enviromental allergic factors in chronic bronchopulmonary disease,* nor does the presence of skin reactivity certify to the importance of an allergic diathesis.

Bacteriological Examination

Adequate bacteriological study of bronchopulmonary secretions is of prime importance diagnostically and as a guide to therapy. A tracheal or bronchial specimen is to be preferred, but, when bronchoscopy is

not feasible, advisable or easily available, the nasopharyngeal contents may be considered a close approximation of tracheobronchial secretion from a bacteriological standpoint. Nasopharyngeal culture can be made from a small cotton pledget affixed to a thin wire inserted through the nostril. It is important that the cotton swab should reach the nasopharynx and not merely the nasal cavity, and that it should be held gently in contact with the posterior nasopharyngeal wall for 30 seconds or more. Alternatively, a throat swab placed in the pharynx will occasionally recover a satisfactory specimen of bronchial secretion when the child coughs.

Direct smear and study of bronchial secretion will be helpful in the diagnosis or exclusion of infections due to acid-fast organisms or fungi. However, the final diagnosis will depend upon the isolation, through culture, of the offending agent. Both aerobic and anaerobic cultures should be carried out routinely, and a culture for fungi always made.

The significance of a potential pathogen isolated from nasopharyngeal secretion cannot be assessed apart from careful clinical appraisal of the patient, the nature and history of the illness, the presence or absence of evidence of acute infection, and the nature of antecedent therapy. A positive bronchial culture is more indicative of active pulmonary infection than a nasopharyngeal or throat culture. In common chronic bronchitis, organisms such as pneumococci, streptococci, *Hemophilus influenzae* and staphylococci are frequently isolated. In fibrocystic disease of the pancreas, *Staphylococcus pyogenes* is most frequently encountered, and after intensive antibiotic therapy there is a strong tendency towards the isolation of *P. aeruginosa*, coliform organisms and *B. proteus*. The resistance of these latter organisms and of many strains of staphylococci to the common chemotherapeutic and antibiotic agents has seriously complicated the therapy of chronic bronchopulmonary disease. Needless to say, potential pathogens isolated from such patients should have their susceptibility in vitro or resistance to available therapeutic agents carefully explored at the time of isolation in anticipation of therapy.

The isolation of *Candida albicans*, unless repeatedly found in pure culture, may have limited significance, owing to the ubiquity of this organism. Other fungi, such as *Nocardia asteroides* or Actinomyces, though occasionally found among the flora of the normal respiratory tract, carry a more certain implication of their etiological role in the patient from whom they are recovered. On the other hand, when *Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformans* or *Blastomyces dermatitis* are found, they may with high degrees of confidence be considered etiological agents in patients with bronchopulmonary lesions.

Other Special Tests

Because fibrocystic disease of the pancreas makes up a large proportion of cases of chronic suppurative bronchopulmonary disease, any child with chronic lower respiratory difficulty of uncertain nature should be studied for the abnormalities associated with this disease. The most helpful tests will be the determination of the sodium and chloride content of perspiration (sweat test) and determination of the effectiveness of fat-splitting activity in the intestinal tract (Lipiodol test). When these tests are abnormal or equivocal, examination of duodenal juices for enzyme content should be carried out to establish the degree of pancreatic involvement which may be present.

Among other diagnostic tests which may from time to time be helpful are routine hematological studies and the determination of serum levels of gamma globulin.

Sweat Test. The content of electrolyte in sweat is abnormally high in 99 per cent of patients with fibrocystic disease of the pancreas. According to the data reported by di Sant' Agnese et al.,[4] sodium and chloride levels in normal sweat average 59 and 32 mEq. per liter, respectively, and range from 10 to 120 in the case of sodium and from 4 to 80 in the case of chloride concentration. On the other hand, in patients with fibrocystic disease of the pancreas di Sant' Agnese et al. found sodium level ranging from 80 to 190 mEq. per liter, with an average of 133, and chloride levels ranging from 60 to 160 mEq. per liter, with an average of 106.

For practical purposes the determination of the sweat chloride concentration alone is an adequate screening test for fibrocystic disease of the pancreas.

A level of 80 mEq. per liter or more of chloride in sweat, when accompanied by evidence of enzyme deficiency in the Lipiodol test, makes the diagnosis of fibrocystic disease of the pancreas virtually certain. However, in rare cases in which there is only partial pancreatic deficiency the Lipiodol test might be misleading.

The collection of sweat samples is a simple procedure and may be carried out in the office or home as well as in the hospital. The technique used at St. Christopher's Hospital for Children is the following:

Technique. The patient's back and anterior trunk are washed with tap water and dried with a clean towel. A 4-inch square of gauze is placed in each axilla. The trunk is then wrapped in a large sheet of plastic material, and the patient covered with a blanket. An ordinary heating pad is then placed underneath the patient. At 15 minute intervals the inner wrap is inspected to see whether sweating has occurred. When droplets can be seen within the plastic cover, they may be collected with a Pasteur pipet. Usually 1.0 ml. will suffice for chloride determination. The procedure should be done with care in small infants and in debilitated patients; water should be offered and hyperthermia avoided.

Lipiodol Test. Silverman and Shirkey[11] have devised a simple test

which takes advantage of the fact that iodine is readily demonstrable in urine after the ingestion of iodized oil, provided pancreatic lipase activity is normal.

Technique. After collection of an initial sample of urine the patient receives oral Lipiodol in a dose of 0.5 ml. per kilogram of body weight, the dose not to exceed 10 ml. or to be less than 4 ml.

A second urine specimen is collected 12 to 18 hours later. Serial twofold dilutions of 0.5 ml. of each specimen are made with 0.5 ml. of water in a series of six tubes. To each tube of diluted urine are added 5 drops of eighth-normal nitric acid, which liberates free iodine, and this iodine is detected by the further addition of 3 drops of 1 per cent suspension of starch.

In children with normal digestion and absorption of fat, free iodine will be found in the second sample to a dilution of 1:8 to 1:32. Failure of demonstration of iodine supposes a disturbance of fat absorption, but is not specific for fibrocystic disease of the pancreas. After this test, it should be noted, serum values for protein-bound iodine may be abnormally high for several weeks.

THERAPEUTIC CONSIDERATIONS

The therapy of chronic bronchopulmonary disorders in children can reasonably be based only on adequate diagnostic study. Not uncommonly, specific therapeutic measures will be indicated which have a high probability of success, such as removal of an unsuspected foreign body, institution of adequate allergic management, periodic administration of gamma globulin to the deficient patient, treatment of a specific infection such as actinomycosis, and the like. Surgical correction of extrinsic bronchial obstruction from tumor or other abnormalities, the surgical removal of localized disease processes or the closure of previously unsuspected tracheo-esophageal communications may produce dramatic relief of distressing symptoms.

In addition to those patients for whom specific curative therapeutic measures are available, there are a large number of patients, such as those with fibrocystic disease of the pancreas, in whom therapeutic measures can be only supportive or palliative, and who suffer relentless progression of generalized suppurative bronchopulmonary disease. It is proposed now to outline measures for symptomatic relief of these patients which may be helpful, as well, for other, more fortunate patients in whom subsequent definitive therapy can be carried out.

The main aims in the management of these patients are (1) treatment of infection, (2) mobilization and removal of secretions, and (3) bronchodilatation in patients with an element of bronchospasm.

Treatment of Infection

Antimicrobial therapy in chronic bronchopulmonary disease must always be based on adequate bacteriological study; this should never omit study of potential pathogens for susceptibility or resistance to chemotherapeutic agents, owing to the prevalence and emergence of resistant

organisms. When an agent is chosen, it should be given in full dosage for an extended time, often by both systemic and local (aerosol) routes.

Acute infections may be superimposed upon chronic infections and are often due to hemolytic streptococci or pneumococci, in which cases penicillin will be the drug of choice, or to *Hemophilus influenzae*, in which case chloramphenicol or a tetracycline derivative may be combined with a sulfonamide for therapeutic effect.

Exacerbations or extensions of chronic infection may be due to these same organisms or to staphylococci or gram-negative bacilli. These may be highly resistant to many antibiotic agents and become increasingly likely to dominate the bronchial flora of the patient with chronic bronchopulmonary disease as he receives chemotherapeutic agents repeatedly or over a long time. Some organisms are susceptible only to antibiotics such as neomycin or polymyxin, which can be safely given over a prolonged period only by aerosol inhalation.

The discovery of specific fungi in bronchial secretion may lead to effective therapy such as the use of sulfadiazine in early nocardiosis, or of penicillin in actinomysis, but in other fungal infections chemotherapy is often ineffective.

Stilbamidine has been used with success in patients with blastomycosis. There is no generally satisfactory agent for treatment of histoplasmosis, though ethyl vanillate has been helpful in some cases.

The recovery of Monilia from bronchial secretion, like that of staphylococci and gram-negative rods, is to be expected eventually in many cases of chronic bronchopulmonary disease. Its role in perpetuation or advancement of the illness is uncertain. A combination of potassium iodide by mouth and sodium caprylate by aerosol inhalation has been effective in pulmonary moniliasis.

New agents, such as nystatin and the amphotericins, have been insufficiently evaluated as yet.

Aerosol Therapy

In many cases of chronic bronchopulmonary disease it is not possible, because of fibrosis or inflammatory processes, to obtain high local concentrations of antibiotic agents through oral or parenteral administration alone. Many workers attest to the effectiveness of administration of drugs through aerosol inhalation under such circumstances.

Penicillin, streptomycin, neomycin and polymyxin are particularly helpful in aerosol therapy, and are often given concomitantly with the systemic administration of these drugs and other antimicrobial agents, the tetracycline derivatives, erythromycin, carbomycin, streptonivicin, chloramphenicol or sulfonamides. Here again, the choice of agent must depend upon adequate bacteriological study.

The technique of aerosol therapy is simple. It requires only a source of compressed air or oxygen, ranging from tank supply of oxygen or motor-driven air compressor to a simple tire pump for manual use, and a nebulizer. Barach[1] showed that the latter should supply particles from 2 to 3 microns in diameter, since these are easiest carried into the lung by the patient's inspiratory effort and produce a high local concentration in the bronchial secretion. A flow of 6 to 8 liters of oxygen per

TABLE 24. *Suggested Dosages and Routes of Administration of Antimicrobial Drugs for Treatment of Chronic Bronchopulmonary Diseases*

ANTIMICROBIAL AGENTS	SYSTEMIC			AEROSOL	
	Routes	Dosage	Intervals	Dosage	Intervals
Sulfonamides	Oral	100 mg./kg./day	4–6 hrs.	—	—
Crystalline penicillin G	Oral IM	30,000 u./kg./day 10,000 u./kg./day or 300,000–600,000 units /day in older children	6–8 hrs. 8–12 hrs.	100,000–300,000 units	6 hrs.
Procaine penicillin G		Same as crystalline penicillin G	24 hrs.	—	—
Streptomycin	IM	40 mg./kg./day or 1 gm./day in older children	12–24 hrs.	200 mg.	6–8 hrs.
Tetracycline and Chloramphenicol	Oral	50 mg./kg./day	6 hrs.	100 mg.	6–8 hrs.
Erythromycin	Oral	30–50 mg./kg./day	6 hrs.	—	—
Carbomycin	Oral	50–100 mg./kg./day	6 hrs.	—	—
Streptonivicin	Oral	40 mg./kg./day	6 hrs.	—	—
Neomycin sulfate	IM potentially toxic	10–15 mg./kg./day	6–8 hrs. not more than 7 days	150–250 mg.	6–8 hrs.
Polymyxin B	IM potentially toxic	1.5–2.5 mg./kg./day	6–8 hrs. not more than 7 days	25 mg.	6–8 hrs.

minute through a Vaponefrin or DeVilbiss nebulizer will supply such a mist, and will nebulize 1 ml. of solution in about 15 minutes.

For administration of aerosol to infants the nebulizer is fitted to a small mask which covers the nasal and oral areas. Older children can make effective use, with instruction and practice, of a Y tube which will permit intermittent nebulization timed to coincide with the inspiratory phase of respiration.

Penicillin may be administered by aerosol in the dose of 100,000 to 300,000 units in 1.0 ml. of distilled water three or four times a day; streptomycin in doses of 250 mg. in 0.5 to 1.0 ml. of solution three times a day, either alone or in combination with penicillin. Polymyxin may be given as 25 mg. in 1.0 ml. of distilled water two to three times

a day. Gibbs[6] used neomycin in concentration of 250 mg. in 1 ml. up to six times daily.

Table 24 summarizes the doses of various drugs currently used.

The duration of systemic and aerosol therapy is variable, but when a certain therapeutic regimen is elected, it should be continued for not less than two weeks. In fibrocystic disease of the pancreas, treatment may be carried on continuously or intermittently for many years and may help maintain the patient in comfort.

Enzyme Therapy

Much interest has been accorded to the use of streptokinase, streptodornase, pancreatic dornase and trypsin for liquefaction of tenacious bronchial secretions. Streptokinase is fibrinolytic; streptodornase and pancreatic dornase depolymerize the desoxyribonucleoproteins which are mainly responsible for the viscosity of purulent exudates. Trypsin has proteolytic effect on proteins, mucin and fibrin.

These enzymes have generally been given in aerosol form in conditions such as atelectasis and other chronic bronchopulmonary diseases.[2, 8] They have generally, but not uniformly, been helpful in liquefaction of bronchial secretions. Untoward reactions include flushing of the face, transient respiratory difficulty and local irritation of the airway after administration of trypsin, and increased production of bronchial secretions after the use of streptokinase and streptodornase.[8] Farber et al.[5] found metaplasia and dyskeratosis of bronchial epithelium after the aerosol inhalation of trypsin and pancreatic dornase.

We have had extensive experience with pancreatic dornase, given both by aerosol inhalation and by direct instillation into the bronchial tree in patients with chronic bronchitis, chronic bronchopneumonia, atelectasis, bronchiectasis and fibrocystic disease of the pancreas. No untoward reaction has been observed, and only transient thinning of sputum has been noticed. We have used doses of 50,000 to 100,000 units in 5 ml. of buffered diluent intrabronchially and 20,000 to 50,000 units in 0.5 to 1 ml. of diluent by aerosol method two to four times daily.

Silbert[10] gave trypsin (Tryptar) intramuscularly to 25 patients with chronic bronchopulmonary disease. He observed both clinical and radiological improvement, but his patients complained of severe local pain at the site of injection.

Bronchodilators

When there is a factor of bronchospasm with obstructive emphysema, inhalation or systemic administration of a bronchodilator, such

as Isuprel, is effective in relieving wheezing and spasmodic coughing spells. The addition of 3 to 5 drops of 1:100 dilution of Isuprel (Isoproterenol hydrochloride) to antibiotic mixtures for aerosol inhalation greatly increases ventilation of the chest.

Mechanical Aids to Bronchial Cleansing

Postural drainage has been traditional in chronic suppurative bronchopulmonary disease, but we have not generally found it very helpful. We teach older children to lie on the edge of their beds and lean over onto a bedside chair for 15 to 20 minutes twice or three times daily. The results are irregular, depending upon cooperation of the patient and his response to therapy.

Bronchoscopic aspiration of mucoid and purulent secretions is often followed by marked clinical improvement. It is especially helpful when obstructive atelectasis has occurred because of tenacious secretions. In severe fibrocystic disease of the pancreas repeated bronchoscopic aspirations may, in skilled hands, contribute greatly to the patient's comfort.

Immunological Therapy

The administration of gamma globulin is specifically indicated, at four week intervals, in patients with agammaglobulinemia. It is unlikely to be helpful otherwise. Autogenous bacterial vaccines are recommended by Wilson,[12] Crump[3] and others for patients with bronchial asthma, but there is no universality of opinion regarding their effectiveness in patients with chronic bronchopulmonary suppurative disease. Our limited experience with autogenous vaccines in these patients has been disappointing.

Mental Hygiene

The chronic bronchopulmonary problems often create complicated emotional reactions in parents and children. The diagnostic and therapeutic measures necessary are at best often uncomfortable and should be carried out with a high degree of understanding and skill if they are to be optimally effective. When the ultimate outlook is unfavorable, as in fibrocystic disease of the pancreas, this fact must be honestly faced with the parents of affected children, not with discouraging nihilism, but with forward-looking emphasis on a general plan of therapy that will attain the child's greatest comfort. It is well never to offer any dogmatic prediction as to the duration of such an illness, which may be many years. Affected children should be expected to enjoy as many normal responsibilities and activities as possible—including school and tolerated exercise.

SUMMARY

Chronic bronchopulmonary disease in children requires a great variety of diagnostic and therapeutic techniques. Therapy must be highly individualized according to the nature of the clinical problem and, when infection is present, can be intelligently planned only on the basis of adequate and continuous bacteriological study.

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HYDROCARBON PNEUMONITIS

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Pneumonic disease in children, when associated with the accidental ingestion of various petroleum hydrocarbons, represents a common pediatric problem. Of the hydrocarbon products available to children—kerosene, gasoline, cleaning fluid, lighter fluid, insect sprays and red furniture polish—kerosene is the most often ingested, accounts for the greater portion of clinical cases, and has been the agent used in experimental studies dealing with hydrocarbon toxicity.

In spite of the fact that the toxicity of hydrocarbon ingestion was pointed out by Hamilton[9] as early as 1897, reports of fatal toxicity continue, and at intervals since then a number of studies concerning children hospitalized because of hydrocarbon ingestion have appeared in the medical literature.

The *clinical findings* in those patients who have ingested a petroleum hydrocarbon product are essentially the same, although they may vary widely in severity. In many cases an initial burning sensation in the mouth and throat is described, followed by gagging, choking and cough. Often the child seems unable to "get his breath" and may show transient cyanosis and dyspnea. Epigastric discomfort and often vomiting soon follow. Drowsiness, muscular twitching and irritability, and rarely convulsions and coma, are distressing signs of central nervous system involvement. Rapid pulse rate and increase in respiratory rate as well as fever may appear within the first few hours following ingestion. Abnormal physical findings in the lung are characteristically meager early in the clinical course, at the same time when roentgenographic exam-

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ination may reveal definite evidence of pulmonary inflammation, often within as short as 30 minutes after the ingestion.

Radiographic abnormalities in the lungs are found in two thirds to three fourths of the children who ingest a petroleum hydrocarbon. These are characterized initially as fine mottled densities extending from the perihilar regions into the lung bases, often with associated peripheral emphysema. The roentgenographic findings may clear in 24 to 36 hours, or progression to confluent densities may occur, representing consolidation and/or atelectasis, usually associated with surrounding areas of compensatory emphysema.

The *mortality* in hydrocarbon poisoning is significant, ranging in published reports from 4 to 10 per cent.

The principal problems presented by these patients are related to the respiratory and central nervous systems. Of the deaths reported, all are due to the development of progressive, severe pulmonary involvement, and none solely to injury of the central nervous system. Aspiration of the hydrocarbon with pulmonary irritation leading to edema, atelectasis and consolidation, often complicated by a secondary or superimposed bacterial infection, is therefore a most pressing problem. The *pathogenesis* of this complication has been difficult to establish, since the patient usually presents the possibility of simultaneous ingestion and aspiration.

The present report is part of a planned study of all cases of hydrocarbon ingestion in children admitted to the in-patient services of the Jefferson Davis City-County Hospital, and covers a three year period. Careful roentgenographic follow-up examinations were carried out in each instance.

On the basis of this experience supplemented by information gleaned from the medical literature an attempt is made to clarify the pathogenesis and to delineate a reasonable plan of management for the patient who has ingested a petroleum hydrocarbon.

PATHOGENESIS

Experimental Studies

The pathogenesis of the pulmonary changes that develop in the wake of petroleum hydrocarbon intoxication in children was studied first by LeGludic et al.[13] in 1914. Using rabbits as the experimental animal, they placed varying doses of kerosene in the stomach by gavage, sacrificed the animals at intervals, and examined them. Marked pulmonary congestion and hemorrhagic necrosis occurred in the rabbits that received relatively large quantities of kerosene (20 cc. per kilogram), but no significant pathological findings were present in the animals that received smaller quantities. The inability of rabbits to regurgitate was thought to preclude the possibility of aspiration. However, as subsequent work by Foley[6] in 1954 indicates, low surface tension petroleum hydrocarbons may be regurgitated even in rabbits.

In 1933 Waring[26] reported the first experimental studies in the United States, in which he summarized experience with 65 cases of kerosene ingestion in young children, two of whom had a rapidly fatal outcome. Stimulated by these observations, he under-

took studies using rabbits as the experimental animal. He concluded that though large quantities of kerosene (30 cc. per kilogram) were well tolerated by rabbits when administered by gavage into the stomach, amounts of 1.2 cc. per kilogram or less, instilled directly into the trachea, produced rapidly fatal pulmonary edema and hemorrhage. These observations led Waring to advise physicians against gastric lavage as a therapeutic measure so as to avoid possible aspiration into the tracheobronchial tree.

In 1943 Lesser et al.[14] reported a fatal case of kerosene poisoning in a two year old child, and described experimental studies on rabbits, in which they found that 16 to 32 cc. per kilogram of kerosene could be tolerated when carefully administered into the stomach by gavage tube, whereas 0.7 to 1.0 cc. per kilogram instilled directly into the trachea produced severe pulmonary irritation. They, too, concluded that the role of aspiration is paramount in the pathogenesis of hydrocarbon pneumonitis and emphasized that animals that received kerosene by gavage in doses larger than are consumed by children had no pulmonary disease. In addition they made the significant observation that positive roentgenographic evidence of pneumonitis usually precedes the appearance of clinical evidence of pulmonary disease, and may in fact be present even in the absence of typical physical findings.

In 1944 Deichmann and associates[4] tested the toxicity of various brands of kerosene, using a dose of 28 cc. per kilogram by gavage in each of 98 rabbits. Mortality rate ranged from 0 to 66 per cent. Their studies suggested that young rabbits exhibited more susceptibility to kerosene than mature rabbits. Further studies with rabbits indicated that the LD_{50} dose for kerosene when given by gavage was 28.4 cc. per kilogram; when injected intraperitoneally, 6.6 cc. per kilogram; and when given intravenously, 0.18 cc. per kilogram. No attempt was made to establish an LD_{50} dose for intratracheal instillation of kerosene. Although the experimental data and results of these studies are similar to those of other investigators, Deichmann et al. interpret their data as evidence for the central role of gastrointestinal absorption of kerosene and concluded that pneumonic disease frequently developed as a result of the pulmonary excretion of the petroleum hydrocarbon.

The most critical experimental studies dealing with the pathogenesis of hydrocarbon pneumonia are those published by Richardson and Pratt-Thomas[22] in 1951. Preliminary studies with dogs indicated that since these animals are capable of vomiting, instillation of kerosene in the stomach allowed regurgitation, and aspiration of the gastric contents tended to occur. Even with ligation of the esophagus after lavage, aspiration of saliva interfered with the studies. This resulted in pulmonary disease due to the aspiration of saliva. Accordingly, they carried out experiments using rabbits and administered kerosene to three groups: one group by gavage tube, another by intraperitoneal injection, and a third by direct intratracheal instillation. Pathological examination of these animals, both rabbits and dogs, revealed that it was virtually impossible, on the basis of histological changes in the lungs, to determine which route of administration had been used. The only possible exception was that vascular damage in the lung was most marked in animals in which the kerosene had been administered intravenously.

On the basis of these studies Richardson and Pratt-Thomas concluded that in order to prove fatal, a large quantity of kerosene would have to be ingested by the child if the toxic effect was a result of gastrointestinal absorption only. In light of observations on animals, a volume in excess of one pint would have to be ingested by an average-sized child in order to produce a fatal effect if the kerosene was absorbed from the gastrointestinal tract only (assuming that no kerosene was aspirated). In striking contrast, very small quantities (one teaspoonful) of kerosene aspirated into the lung could lead to severe pulmonary irritation, edema and hemorrhage, and might even account for a fatal outcome. They conclude that the "primary concern . . . is the danger of aspiration rather than consideration of the possible role of absorption of the hydrocarbon from the gastrointestinal tract." In the light of these findings the authors advocate that lavage should be used infrequently and with caution, and only when the quantity of hydrocarbon consumed is known definitely to be large. When lavage is indicated, great care must be exercised to minimize the possibility of aspiration during the maneuver.

In experimental work with rabbits Foley et al.[6] eliminated the possibility of aspira-

tion by carefully ligating the distal esophageal segment after gavage administration of kerosene (25 to 50 cc. per kilogram) had been accomplished through an incision in the esophagus. In these animals, in which all possibility of pulmonary aspiration was eliminated, no pathogenic changes were noted in the intestines, lungs or viscera. Intense congestion, but no hemorrhagic tendency, was noted in the brain.

Clinical Reports

The clinical evaluation of patients who have ingested various petroleum hydrocarbons, principally kerosene, provides information which has proved useful in delineating the pathogenesis of pulmonary complications. No effort will be made to review in detail the many excellent clinical studies of hydrocarbon ingestion; however, the findings in these studies may be summarized as follows:

In most instances the patient is seen by a physician within one to two hours after ingesting the hydrocarbon product. The history almost invariably includes the story of immediate onset of choking, coughing and gagging, often associated with frank respiratory embarrassment. These symptoms indicate early tracheobronchial involvement, and therefore suggest aspiration. Frequently epigastric discomfort follows, and vomiting occurs with risk of further aspiration. Soon thereafter the clinical picture may be dominated by central nervous system complications, such as lethargy, convulsions and coma. At the time of admission the patient is frequently quite lethargic, and a strong odor of kerosene or other hydrocarbon can be detected on his breath. Physical examination may reveal little else than rapid respiration. The lung fields are usually clear at this stage of the illness. Roentgenographic examination of the chest, however, reveals an early peribronchial pneumonitis in a significant number of cases, sometimes as little as 30 minutes after ingestion of the hydrocarbon. In some cases the lung fields may appear clear, tending to lead the physician into an attitude of unwarranted complacency, and need for hospitalization and prophylactic antibiotic therapy may be ignored. If serial roentgenographic examinations of the chest are made, the majority of these children will show patchy pneumonitis involving both lung fields within the first 12 hours after ingestion.

Early in the clinical course the pneumonitis is typically that of aspiration pneumonitis; later, if no prophylactic antibiotic therapy is instituted, progressive bacterial pneumonia tends to develop.

CLINICAL STUDIES

Material and Methods

These studies were carried out in a large city-county hospital serving the indigent members of a population area of approximately two mil-

lion people. In the course of an average year approximately 100 children are seen in the pediatric clinic or emergency room because of known or suspected hydrocarbon ingestion. In 1953 a program was undertaken to accumulate data on the influence of certain factors upon the course and prognosis of these patients. All children known to have ingested a hydrocarbon were immediately admitted to the hospital. Chest roentgenographic examination was carried out prior to admission to the inpatient service and when possible was repeated at two, four, eight, 12, 24 and 48 hour intervals thereafter. If pneumonitis appeared within this interval, repeated roentgenographic studies were made daily until the lung cleared. Gastric lavage and the induction of emesis were not recommended. All patients received an antibiotic preparation in full therapeutic doses (e.g., penicillin, oxytetracycline, chlortetracycline or tetracycline) as a means of preventing the development of secondary bacterial pneumonitis. To establish the relative value of clinical and roentgenographic examination in the detection of pulmonary inflammation, careful record of the physical findings in the chest was made prior to each roentgenographic examination. Oxygen mist, parenteral fluids and other supportive therapy were used as indicated by the needs of individual patients. All patients were followed up in the out-patient department for two to four weeks after discharge from the hospital.

Results

The 149 patients included in this study ranged in age from nine months to six years, with an average age of 23 months. Seventy were males and 79 were females. There were 29 white children and 120 colored children. This ratio of white to colored is in keeping with the incidence of white to colored applying for admission to our general pediatric clinic. The weight of the patients varied from 7 to 31 kilograms, with an average weight of 12 kilograms. Sixty-eight per cent of the admissions occurred during the period April through September. Of the 149 patients, 56 per cent consumed kerosene, 18 per cent ingested gasoline or lighter fluid, 12 per cent took an insect spray in hydrocarbon vehicle, and 14 per cent drank a "red furniture polish." The quantity of petroleum hydrocarbon ingested was known or could be estimated in 97 patients (65 per cent) and averaged 36 cc., with a range of 5 to 250 cc.

It is noteworthy that the patient who consumed the largest amount, 250 cc. (17 cc. per kilogram), was a 15-kilogram colored female infant who vomited immediately, but was not lavaged. Some 4 to 6 hours later she became lethargic and was brought to the hospital. Except for lethargy and a mild fever (101° F. per rectum), she did not appear ill. Serial roentgenographic examinations of the chest revealed only minimal evidence of pneumonitis 12 hours after ingestion which cleared in 24 hours. Her subsequent course was uneventful.

The patients were brought to the hospital within an average of 2.5 hours of ingestion (range 0.5 to 24 hours), 65 per cent being seen within two hours. Coughing, gagging or choking was an initial symptom in 95 per cent of the patients. Fifty-six per cent of the patients vomited either spontaneously or after induction of emesis at home through digital gagging or the administration of home remedies. Evaluation of the relation of the incidence of vomiting to the volume of hydrocarbon consumed revealed that the patients who vomited drank an average of 33.6 cc., while the patients who did not vomit took an average of 32.4 cc. In 66 per cent of the patients some evidence of central nervous system depression appeared; in 15 per cent it was marked, and in 6 per cent frank coma ensued. This depression usually appeared

TABLE 25. *Summary of Radiographic Studies in 97 Patients Who Had Pneumonia, to Show Probability of Demonstrating Pulmonary Inflammation by Radiographic Examination of the Chest*

ELAPSED TIME RADIOGRAPHIC EXAMINATION			
	Total Patient Examinations	Pneumonia	
		Number	Per Cent
1 hour	31	19	61
2 hours	25	22	88
4 hours	42	38	91
8 hours	25	23	92
12 hours	50	51	98

in one-half to one hour. In mild cases it disappeared within the first 12 to 24 hours, but in others it lasted several days. Elevation of body temperature above 100° F. was a common finding, being present in 24 per cent of the patients on admission and appearing later in 52 per cent more, making a total of 76 per cent. In the majority of patients the temperature was normal by the second or third hospital day. On admission the pulse averaged 135 per minute (range 88 to 180) and the respirations 44 per minute (range 20 to 100). Sixteen patients (11 per cent) presented some evidence of pulmonary disease by physical examination at the time of admission. Of the 97 patients who had roentgenographic evidence of pulmonary inflammatory disease, only 25 per cent had abnormal physical findings in the lungs.

Chest roentgenographic examinations were carried out at the time of admission on all patients. This first roentgenographic examination was performed within 0.5 to 12 hours, an average of 2.5 hours following hydrocarbon ingestion. Table 25 shows the influence of time of examination upon the incidence of roentgenographic evidence of pulmonary inflammation. Of the 97 patients (65 per cent) who showed some roentgenographic evidence of pneumonitis, all but one did so by

the twelfth hour. It should also be noted that of the patients who subsequently had evidence of pneumonitis and were examined within the first two hours, 88 per cent already had definite roentgenographic findings characteristic of pulmonary involvement.

The incidence of pneumonitis was evaluated with regard to the petroleum hydrocarbon consumed by the individual patient, and no significant differences were found (Table 26).

Study of the morbidity and incidence of pneumonitis in patients who either vomited or were lavaged as compared to those who experienced no vomiting or lavage reveals that 55 per cent of the patients in the second group had pneumonitis and remained in the hospital for four days on the average. In contrast, 71 per cent of the patients who either

TABLE 26. *Morbidity Associated with the Ingestion of Various Petroleum Hydrocarbon Products*

PRODUCT	NUMBER OF PATIENTS	MORBIDITY (DAYS)
Kerosene	81	5.1
Gasoline or lighter fluid	28	4.3
Insect spray in kerosene	18	5.1
Red furniture polish:		
Kerosene base	10	4.2
Mineral seal oil base	10	7.5
	Average	5.0

vomited or were lavaged had some evidence of pulmonary inflammation and remained in the hospital an average of five and one-half days.

In an effort to evaluate further the factors contributing to the pulmonary complications the patients were separated into three groups on the basis of their chest roentgenographic examinations (Table 27). No statistically significant differences between the average values for the three groups were found.

Laboratory studies revealed no significant abnormalities in the routine analysis of random urine specimens. The peripheral blood examinations on admission revealed hemoglobin values ranging from 6.0 to 13 gm. per 100 ml. with an average value of 9.7 gm. The white blood cell counts varied from 5000 to 45,000 with an average value of 13,000 per cubic milliliter. There were from 50 to 92 per cent polymorphonuclear cells.

These patients remained in the hospital for two to 15 days, an average stay of five days. Patients were not discharged if they had either clinical or roentgenographic evidence of pulmonary disease.

Two deaths occurred in this series of cases, giving an over-all mortality rate of 1.3 per cent.

The first fatal case was that of a 14 month old white male infant who became ill after the ingestion of approximately 2 ounces of a red furniture polish. This patient

TABLE 27. *Summary of Findings in 147 Patients* Who Ingested a Petroleum Hydrocarbon Product*

		PULMONARY CHANGES	
	None	Mild	Moderate to Severe
Number*	54	57	36
Product:			
Kerosene	60%	62%	36%
Gasoline or lighter fluid	20%	13%	24%
Insect spray in kerosene base	10%	11%	18%
Red furniture polish:			
Mineral seal oil base	2%	8%	18%
Kerosene base	8%	6%	4%
Volume consumed (av.)	29 cc.	39 cc.	26 cc.
Time to hospital (av.)	3.5 hrs.	2.4 hrs.	3.4 hrs.
Initial gag, choke, cough	88%	98%	94%
Vomiting and/or lavage	60%	60%	73%
Central nervous system depression	56%	72%	60%
Admission temperature (av.)	99.3°F.	99.8°F.	100°F.
Maximum temperature (av.)	100.7°F.	101.5°F.	101.8°F.
Time to maximum temperature (av.)	12.6 hrs.	9.4 hrs.	15.8 hrs.
Duration of hospital stay (av.)	3.8 days	5.5 days	6.4 days

* 2 fatal cases omitted.

experienced severe coughing, gagging and choking initially, followed within a few minutes by marked lethargy progressing to stupor. He did not vomit. Because of the severe central nervous system depression he was brought to the hospital 5 hours later. A chest roentgenogram was taken, and copious gastric lavage was then performed in the emergency room. This initial roentgenographic examination revealed bilateral pulmonary infiltration characteristic of aspiration pneumonia. In the hospital parenteral antibiotics were begun, and he appeared to be improving until the second hospital day, when the temperature rose to 102° F. and respirations became more labored. He was given supportive and symptomatic therapy, but became progressively worse and died on the fourth hospital day.

The second fatal case is of particular interest since this 18 month old colored male child is the only patient in this series who made no attempt to "drink" a petroleum hydrocarbon product. This child reached onto a table and pulled off a quart can containing kerosene, which showered directly into his upturned face. He immediately had severe coughing, gagging and choking, and there was marked irritation of his eyes and face. He did not vomit and was not lavaged. Stupor appeared within 15 minutes, and he was brought to the hospital approximately one hour later in a semicomatose state. Respirations were rapid, but there was no other evidence of pulmonary involvement. Roentgenographic examination at the time of admission revealed bilateral peribronchial infiltration extending into both bases with marked peripheral emphysema. In spite of antibiotic and supportive therapy this patient suffered progressively severe dyspnea and tachycardia, and died 6 hours after admission.

DISCUSSION

In recent years the widespread use of catalytic cracking processes designed to increase the commercially useful yield from crude oil has increased the great variety of petroleum hydrocarbons present in various distillate fractions. In addition, since the composition of the final prod-

uct varies with the source of the original crude oil, it is not surprising that the toxic manifestations vary from patient to patient, and from region to region of the country, depending on the products used. Furthermore, *the petroleum hydrocarbons are not pure chemical compounds, but represent a mixture of saturated and unsaturated hydrocarbons of the aliphatic and aromatic series and are separated only as fractions distilled under certain specified temperature ranges.* Most have relatively low volatility. Since kerosene is used principally as fuel oil, it is washed with sulfuric acid to remove unsaturated hydrocarbons that tend to leave a gummy residue after combustion. However, large numbers of cyclic compounds, many of which are closely related to anesthetic agents commonly used in medicine, remain in the market products and account for the high incidence of central nervous system depression in patients who have ingested a product containing petroleum hydrocarbons.

The patients in this series took products composed principally of petroleum hydrocarbons accidentally in each case. Carelessness in the home was the main factor involved, since, unfortunately, these hydrocarbon products were frequently easily available to the child in such familiar and attractive containers as milk and soft drink bottles. Storage areas for kerosene, gasoline, insect spray, furniture polish and the like were often well within the reach of the toddler.

The most prominent finding—pulmonary inflammation—was present in 65 per cent, progressing to consolidation in 35 per cent and terminating in death in 1.3 per cent. *Physical examination of the lungs is not a sensitive method for the detection of early or minimal degrees of chemical pneumonitis, and roentgenographic examination of the chest is an essential diagnostic measure.*

Although most patients consumed only one or two mouthfuls, the history of gagging, choking or coughing in 95 per cent of the cases suggests strongly that aspiration of the hydrocarbon at the time it was ingested was an important factor in the pathogenesis of pulmonary disease. Vomiting, often associated with a second episode of choking and coughing, occurring within a few minutes to two hours following ingestion in 56 per cent of the cases, emphasizes further the probability that aspiration occurred prior to hospital admission. Information available from the histories of patients in this series suggested that aspiration was present in 95 per cent prior to the time they were seen by a physician.

The extremely rapid development of an inflammatory process in the lungs as evidenced by early roentgenographic changes suggests that the pathological process in the lung must begin almost immediately after ingestion. Such a temporal relationship suggests that the irritating hydrocarbon gains direct access to the tracheobronchial tree rather than

by the indirect route of gastrointestinal absorption, hematogenous transport and pulmonary excretion into the pulmonary tissue. This view tends to be supported by clinical experience, since it has been observed that if no radiologic evidence of pulmonary involvement appears by the end of the first 12 hours, it is not likely to develop later. Central nervous system depression also appeared early, and often disappeared by the time the patient was admitted to the hospital. There was no essential difference in the morbidity in groups who received antibiotic therapy before or after three hours of ingestion, since, of the 120 patients receiving antibiotics in less than three hours, the morbidity was five days, and in the smaller group (27 patients) who received antibiotic after three hours, 5.7 days.

Initial management of the child with hydrocarbon pneumonia has been the subject of much discussion. Disagreement is largely centered about the pathogenesis of the pulmonary complications and is based upon the interpretation of the clinical and experimental studies. Some authors advocate that if the patient is seen within one to two hours after ingestion of the hydrocarbon, gastric lavage should be carried out immediately. Others are equally firm in advising against this procedure, since, in their opinion, lavage increases significantly opportunity for aspiration of the hydrocarbon. All recommend that if lavage is carried out, it should be done with utmost caution so as to prevent further aspiration. This includes placing the child face-down over the parent's knees in the "spanking" position, and the careful insertion of a lavage tube. The lavage fluids suggested range from tap water to mineral oil. Since petroleum hydrocarbons are soluble in mineral oil and the latter is not absorbed from the gastrointestinal tract, mineral oil seems a logical choice for lavage. In the experience of our groups, lavage of the stomach is usually unnecessary, since either the amount ingested is small or the patient has already vomited before he is seen by a physician. The added hazard of aspiration incident to even the most expert lavage far outweighs the potential danger of gastrointestinal absorption.

Antibiotics, used in full doses to prevent the development of secondary bacterial pneumonia, are an essential part of the management of patients who have ingested petroleum hydrocarbons. A broad-spectrum antibiotic has been used by most authors. In the present studies penicillin was given to a majority of the patients and appeared to be an effective agent. Since the chemical pneumonitis which predisposes to the bacterial pneumonia does not reach its peak of development for 24 to 48 hours in most patients, it is felt that all patients should receive antibiotic therapy for at least 72 hours, or until all evidence of pneumonitis has disappeared.

In our experience the administration of central nervous system stimulants has not been necessary. Other symptomatic treatment such as

oxygen, humidity control and use of parenteral fluids should be given as the condition of the patient indicates.

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PULMONARY TUBERCULOSIS:

THE PRIMARY LESION

Specific vs. Nonspecific Therapy

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The battle against the "white plague" entered a new phase with the advent of the era of "specific" antimicrobial therapy. In no phase of tuberculosis have our concepts of treatment been more greatly disturbed by this new approach than in primary tuberculosis in childhood, particularly since in this form of the disease it has been necessary to establish not only the effectiveness of specific therapy, but also, and more fundamentally, the actual need for it.

To delineate this problem more precisely it would seem desirable first to define the primary lesion of tuberculosis and then to discuss its prognosis, as we know it today.

DEFINITION

In this country the primary lesion of tuberculosis is pulmonary in about 95 per cent of cases, resulting from the inhalation of droplet nuclei containing living virulent tubercle bacilli. This lesion, developing within two to six weeks, has been well described as the "primary complex," an area of parenchymal pneumonia plus enlargement of the regional or hilar lymph nodes. Coincident with the development of the primary complex, and about four to six weeks after the onset of the infection, the tuberculin test becomes positive. In the majority of cases this entire process is attended by few, if any, symptoms and then goes on to a slow and asymptomatic healing over a period of six to 24 months.

There are, however, cases in which the primary disease may be responsible for more serious trouble. The mechanisms for this are

(1) bacterial multiplication and progressive destruction at the initial site; (2) erosion of a bronchus by enlarged, infected hilar lymph nodes with bronchogenic spread (endobronchial disease); (3) hematogenous spread of tubercle bacilli throughout the body. As for the last mechanism, even with the asymptomatic and "benign" development of a primary complex there frequently occurs also a lympho-hematogenous dissemina-

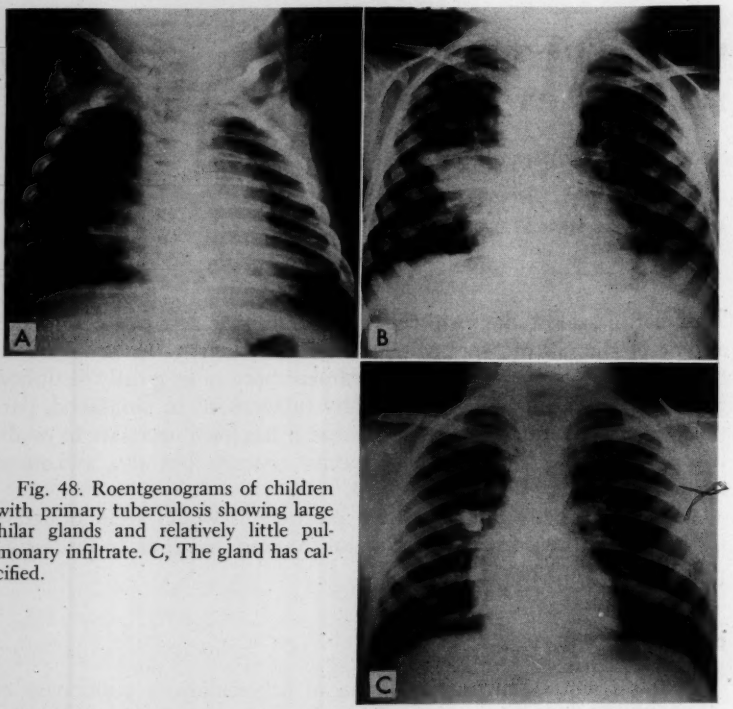

Fig. 48. Roentgenograms of children with primary tuberculosis showing large hilar glands and relatively little pulmonary infiltrate. *C*, The gland has calcified.

tion resulting in the formation of the tubercles often found in distant organs.[9, 10, 42] These tubercles remain the repository nests of viable tubercle bacilli which may reactivate years later to cause clinical disease.

The size of the primary lesion varies from one too small to be seen by x-ray to one readily seen by x-ray, involving a large portion of a lobe. More commonly, however, especially in younger children, the hilar lymph nodes are visibly enlarged, while the primary parenchymal lesion remains invisible on x-ray (Fig. 48). Frequently the enlarged hilar nodes will interfere with the patency of a bronchus, either by extrinsic pressure or by erosion through the bronchial wall with partial or complete

obstruction of the bronchus by incompletely discharged necrotic debris. Varying degrees of atelectasis and pneumonitis or of obstructive emphysema result (Figs. 49, 50) all of which are included in the clinicopathological designation of endobronchial disease.[24, 25, 31] Since these represent mechanical lesions resulting from interference with the circulation of air through a bronchus, they are best not regarded as evidence of progressive tuberculous disease, but as part of primary pulmonary tuberculosis.

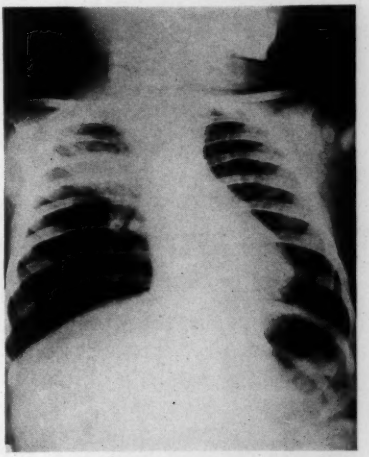

Fig. 49. Endobronchial disease with atelectatic pneumonitis in the right upper lobe and obstructive emphysema involving the right middle and right lower lobes. Note shift of the mediastinum to the left.

PROGNOSIS

One reason for our dilemma in trying to decide whether or not to treat primary tuberculosis with antimicrobial drugs is its seemingly good prognosis without treatment. A more careful examination, however, reveals that this is not so. In fact, there would be no other forms of clinical tuberculosis in children or adults if human beings did not get primary tuberculosis.[18] As will be discussed later, many factors affect the prognosis of tuberculosis in different groups of children.

More specifically, one may separately consider the immediate and the delayed prognoses according to a timetable which the natural history of the disease would tend to establish.[18, 36, 53, 55]

In an unknown but large proportion of children, about two to four weeks after the onset of infection there is a general febrile reaction with malaise and occasional joint or muscle pain, which usually abates within a month. When this "fever of onset"[36] persists for a longer

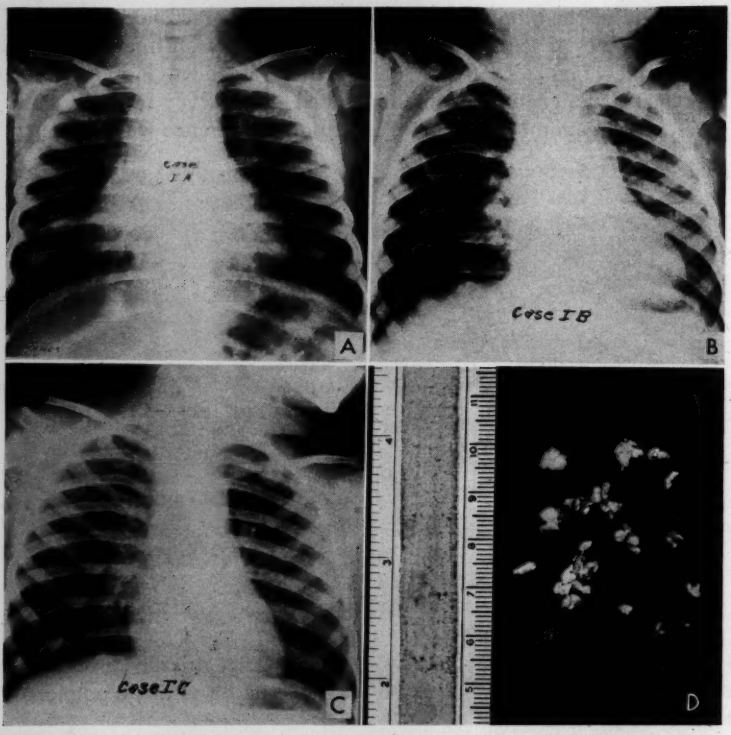

Fig. 50. *A, B, C,* Varying stages in the course of endobronchial tuberculosis in a 2 year old child admitted to hospital with a localized and persistent wheeze in the right chest and a presumptive diagnosis of aspiration of a foreign body. On bronchoscopy the caseous material shown in *D* was removed from the right main bronchus. *A,* Atelectasis of the right middle lobe. *B,* Obstructive emphysema with shift of the mediastinum to the left. *C,* Return of the mediastinum to the midline after repeated bronchoscopies.

period, progressive disease should be suspected according to the following timetable:

1. Tuberculous pneumonia consisting usually of a large area of caseous destruction occurring by contiguous spread from the original parenchymal lesion.
2. Miliary tuberculosis or tuberculous meningitis usually coming on within three to nine months after tuberculin conversion. However, *the particularly malignant meningitic form may also occur at any time in a person's life,* when a previously quiescent tuberculoma in the brain is for some reason activated, swells and ruptures into the meninges. According to Debré[9] the risk of tuberculous meningitis developing after tuberculin conversion in childhood is 0.33 per cent.
3. Pleurisy usually starting three to seven months after tuberculin conversion. It is extremely rare for someone who has had pleurisy to succumb to meningitis. However, pleurisy has its own bad prognosis in that a large percentage of pa-

tients with pleurisy (untreated by specific drugs) are said eventually to acquire reinfection (chronic pulmonary) tuberculosis.[48]

4. Endobronchial tuberculosis, with atelectasis or obstructive emphysema, or both, which in its strictest sense is not an evidence of progressive tuberculosis, usually also develops within three to seven months after conversion.[55]
5. Bone and joint tuberculosis develops in most cases during the first year after the primary infection, in a considerable number during the second, and most of the remainder in the third.[55]
6. Renal tuberculosis in most cases will become manifest three to 15 years after primary infection.
7. Chronic pulmonary tuberculosis or reinfection tuberculosis may occur at any time from immediately after the primary infection of the adolescent or the young adult to 30 to 40 years after the primary infection of childhood. *This type of the disease,* commonly thought of as one of the great scourges of the earth, *is still a consequence of primary pulmonary tuberculosis.* According to Debré,[9] 5 per cent of children with positive tuberculin tests will have this condition between 15 and 20 years of age.

It is evident that the prognosis in any specific case is better assessed by knowing in which of the foregoing chronological stages the patient falls.

The prognosis of untreated primary infection and the likelihood of the development of some of the complications are affected by various factors, some relating to the host, others to the parasite.

Host Factors Affecting Prognosis

AGE. Age is an important factor affecting prognosis, infancy and adolescence representing danger periods (Fig. 51) in which likelihood of the development of progressive disease is greater.[17, 53]

Several studies have shown that the highest mortality rates, up to 30 per cent, occur in the first year of life,[36] and especially during the first six months.[7, 30] In Edith Lincoln's series of 980 cases before 1947 the highest death rates were in the youngest children.[28] The percentage drops slowly until the second year and then drops sharply from three to 10 years, the so-called golden age of tuberculosis. However, the immediate risk of progressive disease rises sharply again in the preadolescent and adolescent periods.[5, 26] In girls there is particular danger in the period from six months prior to until six months after the menarche.[29]

FAMILY BACKGROUND. There would seem to be little question that the child whose family has had a lot of tuberculosis is more likely to have a larger primary lesion and a poorer ultimate prognosis than the child infected by casual contact.[2, 5, 9, 16] Factors involved in this are (1) hereditary lack of resistance, (2) frequent exposures.

RACIAL BACKGROUND is of some importance, possibly for reasons similar to family background. At any rate it appears that in this country

Negroes, Spanish-Americans and Irish have poor resistance to the disease. Whether this is an environmental or truly racial factor remains undecided.[6]

AGE OF INFECTION when disease is diagnosed is an important prognostic factor. The first six to 12 months after the onset of the disease (particularly the first six months) are the most hazardous and are the period during which progressive disease is the most likely to occur.

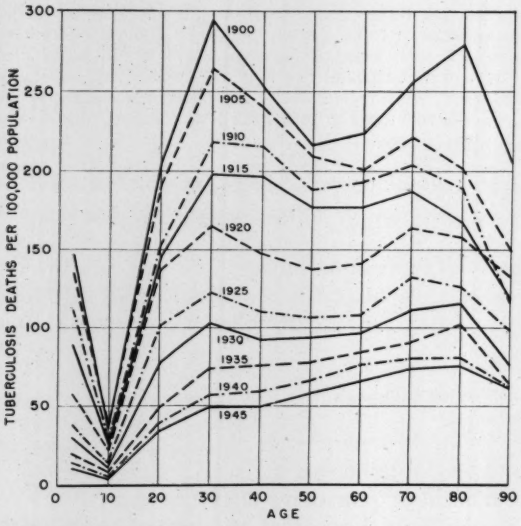

Fig. 51. Death rates for tuberculosis by age: death-registration states, quinquennial years, 1900–40. Note increased death rate in infancy and adolescence. (From *U. S. Pub. Health Rep.*, 1948.)

INTERCURRENT INFECTIONS, most particularly measles, may cause exacerbation and progression of previously quiescent primary disease. The pathogenetic mechanism for this is not known, but it may be related to the temporary tuberculin anergy which may occur in a tuberculin-positive person who has measles. Rich, however, rejects this explanation.[45]

Similarly, intercurrent surgery or steroid therapy in the presence of an active tuberculous lesion may cause spread of the tuberculosis.

NUTRITION, or rather undernutrition, may increase susceptibility to disease. Wartime statistics of the rising incidence of tuberculosis in famine-ridden countries bear witness to this. In this regard, also, Johnston's nutritional investigations on adolescent girls, in whom the prognosis of primary tuberculosis is relatively poor, are of no little interest.[20, 21]

Factors Related to the Parasite Affecting Prognosis

The "infectivity" and over-all pathogenicity of the mycobacteria which cause tuberculosis vary widely from strain to strain, and may vary independently. These properties of the parasite undoubtedly contribute to the prognosis in a complex fashion. Suffice it to note that many isoniazid-resistant mutants of tubercle bacilli have had high infectivity but low over-all pathogenicity for experimental animals.[50]

These factors take on particular importance since children are likely to be exposed to adults who have previously been treated (possibly inadequately) and who may be excreting isoniazid-resistant mutants of tubercle bacilli.

IMPORTANCE OF THE CONTROL OF PRIMARY TUBERCULOSIS IN THE CONTROL OF TUBERCULOSIS IN GENERAL

With our present knowledge it would seem that the most effective way to combat the problem of clinical tuberculosis is to attack the vast reservoir of tubercle bacilli represented by all the people, especially the children, with positive tuberculin tests, since they represent the group from which the aforementioned "complications" of primary tuberculosis will derive.[13] Because the immediate danger of progressive disease is worst during the first year after infection,[28, 29] it becomes imperative to attack this reservoir as early as possible.

In other words, one method of assault upon the problem of tuberculosis which is uniquely suited to the physician caring for children is the early identification of the child who harbors tubercle bacilli by including the routine use of the tuberculin test in well-child care.[35] This early identification has the following advantages:

1. By x-raying the contacts of the child who has converted to a positive tuberculin, the physician is in an excellent position to find the person (usually an adult) with "open" tuberculosis who infected his patient, thus identifying and removing from circulation a previously unknown and infectious case of tuberculosis. The younger the child, the more likely is the contact to be some member of the immediate family. The index of suspicion should always be high for grandparents,[38] with their smoldering low grade disease evidenced only by a "cigarette cough," and for baby sitters. During the year 1953 baby sitters were the source for 12 different cases of primary tuberculosis referred to the Denver Tuberculosis Dispensary!

2. Another advantage of routine tuberculin testing is that by finding and keeping track of the tuberculin-positive children one delineates that group in which different types of clinical tuberculosis will develop; hence it will be possible to diagnose and treat these cases early.

3. The third advantage of finding recent convertors by routine tu-

berculin testing is that these are probably the persons most susceptible to antimicrobial therapy—in whom the tubercle bacilli are still actively multiplying and in whom few if any irreversible tissue changes have occurred. In fact, in four very early convertors I was able to revert the tuberculin test to negative, thus presumably reducing the number of viable tubercle bacilli to a minimum.[46]

In summary, then, the general practitioner and the pediatrician have a signal opportunity to identify the contagious forms of tuberculosis in the community by including the routine use of the tuberculin test in well-child care. I recommend that this procedure be done at yearly intervals, and possibly twice during the first year, when tuberculosis has such a serious prognosis.

METHODS OF TUBERCULIN TESTING

The most convenient and accurate procedure thus far devised has been the use of freshly and properly prepared old tuberculin 1:1000 (preferably made every three months with a buffered diluent* and tested for potency on guinea pigs) or the new intermediate strength P.P.D. which maintains its strength for one week after being put into solution. The patch test has elicited too many falsely positive reactions; too often it gives equivocal results which are difficult to interpret. The presence of at least 5 mm. of induration (with or without erythema) occurring 48 hours after the intradermal instillation of tuberculin indicates a positive reaction.

If tuberculosis is strongly suspected in a given patient, a freshly prepared and more dilute solution of old tuberculin or P.P.D. should be used first.

ANTITUBERCULOUS VACCINATION

No discussion of the prevention of the complications of primary tuberculosis in children would be complete without mention of BCG and the vole bacillus vaccine. The reader is referred to the recent important literature on this subject for a more thorough consideration.[19, 49, 56] Suffice it to say here that although BCG has the disadvantage of elimi-

* Procedure for preparation of diluent:

A. Make a concentrated stock solution:
   Na_2HPO_4—14.2 gm.
   NaCl—80.0 gm.
   Aq. Dist. qs 1000 ml.
   Adjust pH to 6.5
   Dispense in small flasks
   Autoclave 10 minutes at 15 pounds' pressure
   Label and store at room temperature.
B. Dilute above with nine volumes of sterile distilled water when ready to add tuberculin.

nating the value of the tuberculin test in routine pediatric care, and for this reason in this country at least would not be recommended for everybody, it still has a place in the protection of those children being raised in a tuberculous milieu. When we have reached that stage of perfection in preventive medical care of children at which we can be assured of identifying and actively treating all children within one to two months of their tuberculin conversion, it is possible that the use of BCG will be outmoded. Until then, however, the fact is most compelling that the proper administration of BCG to tuberculin-negative children likely to be heavily exposed to tuberculosis will prevent the development of the most malignant forms of progressive primary tuberculosis, especially meningitis.

The question of chemoprophylaxis with isoniazid for infants born of tuberculous parents is one which, although not yet answered, warrants serious consideration.

MANAGEMENT OF PRIMARY TUBERCULOSIS

Specifically, the problem is: Should primary tuberculosis be treated with antimicrobial drugs, and if so, with what drugs, with what dosages and for how long? The question by its very simplicity leads us into a trap all too frequent in clinical medicine, namely, that of dealing with the disease, primary tuberculosis, rather than with the child with primary tuberculosis. With our present knowledge the question (one of the most fundamental and pressing questions in tuberculosis and in pediatrics today) cannot be answered. It is under active investigation now, both in this country and in France.[9, 11, 15] Because of the many variables affecting prognosis, an extremely large, carefully controlled series using different drugs and dosage schedules and followed over many years will be needed before a definite answer may be justified.

However, the practicing physician, faced with a child with primary tuberculosis now, must answer this question to the best of his ability for his patient. It is the purpose of this paper to give him practical guidance in this regard.

There are certain good and some bad things we know about the specific treatment of primary tuberculosis which should affect any decisions one may be presently faced with, namely:

1. There have been no authenticated reports to date of tuberculous meningitis in a child *adequately* treated for primary tuberculosis with isoniazid.* By *adequate* treatment reference is meant particularly to dos-

* Since this paper was written a report by Dr. Edith Lincoln[32] states that one of her patients acquired meningitis while on isoniazid therapy for primary tuberculosis. It seems most likely that this child received *inadequate* therapy, especially since organisms obtained from the cerebrospinal fluid were sensitive to isoniazid.

age and duration of therapy, both of which will be discussed later. This, of course, was not true prior to the use of isoniazid and is a fact of great importance.

2. There has been a great decrease in the incidence of other forms of progressive primary tuberculosis, coincident with the more widespread use of antimicrobial agents, especially of isoniazid. Whereas four years ago approximately 40 per cent of the pediatric beds at the National Jewish Hospital were occupied by patients with some form of osseous tuberculosis, today not more than three or four of 50 patients have bone tuberculosis. This has been the experience of others also.[3, 12, 47]

3. On valid theoretical grounds it would seem that the institution of antimicrobial therapy, particularly early in the disease when the tubercle bacilli are actively multiplying (i.e., when they are most susceptible to the bactericidal action of isoniazid), should diminish the population of tubercle bacilli remaining alive within the body to cause trouble later.[37, 57] There is some evidence that the likelihood of the development of reinfection tuberculosis depends to some degree on the number of tubercle bacilli remaining dormant in the body after the active primary phase is over.[2, 9]

4. It appears logical that, as in other infectious diseases, the earlier in its course tuberculosis is treated with a potent antimicrobial, the more effective the antimicrobial will be in preventing subsequent endogenous exacerbation, particularly after some host responsiveness has developed, as indicated by a positive tuberculin reaction in the case of tuberculosis. The recent report of our success in reverting to negative four children whose tuberculin reactions had just turned positive is consistent with these views on the effectiveness of early therapy.[46]

In summary, then, what one would hope to accomplish by treating primary tuberculosis might be listed as follows:

1. Shortening the period of morbidity during primary disease. Some workers[9, 11, 22] feel definitely that both clinically and radiologically this occurs. Others[2, 16, 28, 47] are not so certain. Some of the differences of opinion may be due to differences in dosages used, the former workers using much larger doses. It is also worthy of note that it is the feeling of many that the tendency of primary tuberculosis to heal with the deposition of calcium is diminished if isoniazid is used in treatment. This may fairly be interpreted as evidence that less extensive foci of residual necrosis follow treatment with isoniazid.
2. Prevention of progressive disease.
3. Decrease in the incidence of reinfection forms of tuberculosis.

The disadvantages which might possibly result from this therapy are:

1. The development of drug-resistant mutants in the body, which might later cause disease which is resistant to therapy. This has rarely been a factor in tuberculosis in childhood and should prove even less important if care is taken to ensure that adequate concentrations of effective drugs reach the tubercle bacilli (see p. 265). There is good evidence that most of the isoniazid-resistant tubercle bacilli which might remain would have a lowered pathogenicity and would probably be incapable of causing progressive disease except in ulcerated lesions.[50] The fact is

important that we have thus far not found microbial resistance to be a significant problem in the children whom we have treated.

2. The psychological trauma, especially to the parents, of giving medication for what has generally been considered a benign condition. We have not found this to be a factor of importance. Parents in general have not become overanxious and overprotective as those of children with possible rheumatic fever often are, and, with a little education, do not feel stigmatized.
3. The encouragement of the promiscuous and improper use of the drugs is a definite danger, as it has been with penicillin in other infections. Isoniazid is a cheap, easily obtained, relatively nontoxic drug usually taken by mouth. It would be easy to use it in improper amounts and with improper indications.
4. Toxicity has proved to be of much less importance, as regards isoniazid, in children than in adults. Even with doses of 20 mg. per kilogram we have seen none of the signs of neuropathy reported in adults.[40] If they should occur, they could be combated by the use of pyridoxine.[40]

The convulsogenic properties of isoniazid in children with previous history of convulsions should be remembered,[41] and it is our practice to put these children also on phenobarbital or Dilantin.

Dihydrostreptomycin has a great tendency to cause eighth nerve deafness, which is permanent.[39] For this reason we do not feel that it should be used either by itself or in combination with streptomycin sulfate. Streptomycin sulfate, even though it may cause vestibular damage, is the preferable drug. Most children seem able to adjust to vestibular difficulties. Sensitivity reactions to streptomycin occasionally occur, but usually do not cause permanent effects, being mostly in the nature of allergic rashes.

Para-aminosalicylic acid is in general nontoxic, except for gastrointestinal upsets in some children. When upsets occur, a period of rest from the drug frequently will suffice and the patient can then tolerate it anew. Occasional skin reactions, especially purpura, may also occur.

Drug Dosages and Schedules in Treatment of Primary Tuberculosis

One important consideration in the use of any antimicrobial agent is whether the drug being taken by the patient is getting to the microorganisms in an active form and in effective concentration.[50]

It has been shown that isoniazid is detoxified in the body by an acetylation mechanism which also inactivates it.[50] The rapidity and degree of this inactivation vary with different patients, as shown by microbiological assay. It is our impression, as yet unverified, that this detoxification process is particularly rapid in many children. There is evidence, however, that para-aminosalicylic acid competes with isoniazid for this acetylation mechanism, and that by giving para-aminosalicylic acid simultaneously with isoniazid the level of *active* isoniazid in the blood is raised.[34, 50]

For this reason the following dosage schedule is recommended when specific therapy is indicated: isoniazid, 16 to 20 mg. per kilogram per day, together with para-aminosalicylic acid, 6 to 10 gm. per day, for one year.

Treatment is given for a year in an attempt to prevent the occurrence of the worst of the early complications, especially meningitis, which usually manifests itself within the first three to 12 months after the

primary infection. Isoniazid is prepared in 50- or 100-mg. scored tablets, is very cheap, and may be given in one or two daily doses. It is also prepared as a more expensive syrup (10 mg. per cubic centimeter) for small infants.

Para-aminosalicylic acid may be administered in tablet form or, less preferably, as a specially prepared elixir* in two daily doses.

The combination of large doses of isoniazid and para-aminosalicylic acid is recommended for all children on whom determinations of blood levels of active isoniazid are not available. If adequate levels of biologically active isoniazid are present in the patient's blood without para-aminosalicylic acid, the latter can be dispensed with. The use of pyridoxine and anticonvulsants with isoniazid has already been discussed.

Streptomycin sulfate is recommended in addition to isoniazid and para-aminosalicylic acid only for those hospitalized children with rather large primary lesions who are clinically ill. The author recommends that it be given in a total weekly dose of 200 mg. per kilogram. This may be administered in biweekly, triweekly or daily fractions, depending on the size of the child.

SUMMARY OF DOSAGE SCHEDULES. *Isoniazid.* Sixteen to 20 mg. per kilogram per day for one year. Add pyridoxine, 10 to 50 mg. per day, if there are any signs of neurotoxicity. Add daily phenobarbital or Dilantin if the patient has a history of convulsions.

Para-aminosalicylic Acid. This is to be used in the absence of evidence by microbiological assay of a level of active isoniazid in the blood of greater than 0.4 microgram per milliliter six hours after a test dose of one half the daily dose of isoniazid has been administered. If used, para-aminosalicylic acid should be given in doses of 6 to 10 gm. per day, or about 200 mg. per kilogram for infants, for one year.

Streptomycin Sulfate. This should be administered intramuscularly in a dose of 200 mg. per kilogram per week in divided doses for one month only in those hospitalized and clinically ill children with large lesions on x-ray examination.

Specific Plan for Management of Primary Pulmonary Tuberculosis in Children

Considering the foregoing discussion, and bearing in mind the limitations of our knowledge, I would make the following specific recom-

* ℞: PAS ..... 100 gm.
NaHCO$_3$ ..... 60 gm.
Methyl salicylate ..... 5 drops
Syrup of cinnamon ..... 165 cc.
H$_2$O qs ad ..... 500 cc.
This 20 per cent solution of para-aminosalicylic acid is stable for only about two weeks.

mendations for the management of primary tuberculosis, defining particularly those cases which should get antimicrobial therapy:

1. Children under three years of age with a positive tuberculin test should be treated.

2. Children from three to 10 years of age should receive specific therapy under the following conditions:

a. If diagnosed within six months of conversion.
b. If they have a strong family history of tuberculosis and especially if, in addition, they belong to one of the racial groups which have poor resistance to tuberculosis.
c. If there is a large lesion of active primary disease on x-ray examination, and they are clinically ill.
d. If they have radiological evidence of a healed primary lesion and then get measles. In this event three months of therapy should be adequate if no evidence of reactivation of the lesion develops within that time.

3. Children from 10 to 16 years old should be treated:

a. If there is a history of tuberculin conversion within one year.
b. If a girl is in the period extending from about six months before to about six months after the onset of the menses and has a history of previously having had radiological evidence of active primary disease, she should be treated for one year because of the tendency for reactivation to occur at this age.[29]
c. If there is definite radiological evidence of active primary infection.

Nonspecific Management of Primary Tuberculosis

Rest. Isoniazid is effective only against the rapidly multiplying tubercle bacilli. For this reason the patient being treated with isoniazid does not require the immobilization previously thought to be so desirable. Physiological and emotional balance are sought by allowing the child to lead as normal and active a life as possible. While he is toxic and febrile he is kept in bed as any clinically ill child is, but when he feels well, he is allowed to be up and around. Under these conditions, i.e., when he feels well, he may go to school. It should be stressed over and over again to both parents and physicians that the child with asymptomatic primary tuberculosis is not contagious or a hazard to other children.

Nutrition. A nutritious diet is of course always desirable. Johnston's work emphasizes the importance of specific dietary instructions for adolescent girls, specifically one quart of milk a day, one portion of fish, meat, cheese or egg at each meal, and 1200 units of vitamin D a day.[20, 21]

Bronchoscopy. This is of some help in diagnosing endobronchial disease and occasionally in relieving a complete or partial obstruction of a bronchus. In general, however, this has not proved to be a very useful therapeutic tool.[24, 25]

Steroids. Steroids are considered by some to be valuable aids in hastening the healing of large hilar glands, especially those that en-

croach on a bronchus.[8] In a relatively few cases I have not been impressed by their efficacy. Antimicrobial therapy, including isoniazid, should always be administered when steroids are given. If steroid therapy is to be discontinued, it is important to taper the drug slowly lest one get a "rebound" type of phenomenon. This occurred in one of our patients, resulting in the sudden appearance of a massive pleural effusion.

SUMMARY

1. The management of primary pulmonary tuberculosis in the child has been outlined with special reference to the use of specific antimicrobial agents.

2. Stress has been placed on individualization of patients, especially as regards age, sex, background, duration of disease and general health in determining therapy.

3. Consideration of "adequacy" of therapy in terms of the *amount of the active principle of the drug* being delivered to actively multiplying tubercle bacilli is emphasized.

4. Mention is made of the inappropriateness of former concepts regarding rest in the treatment of tuberculosis, especially in the child.

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PERTUSSIS

Current Status of Prevention and Treatment

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The rate at which so-called modern medicine is moving forward, not only in basic sciences, but also in many aspects of clinical practice, is reflected in the changing picture in the type and the severity of illnesses seen in doctors' offices as well as the predominant case categorization of hospital wards. Communicable disease used to account for so much severe illness that special hospitals had to be built for them in many areas. The empty contagious wards and reassignment of the bed space to other types of illness indicate that the "black diphtheria" and hemorrhagic scarlet fever that our parents knew are diseases of the past.

Whooping cough, or pertussis, has followed the general trend in this changing picture, but continues to occupy an important position in respect to mortality and morbidity in the first year of life. It causes more deaths in this age group than measles, scarlet fever, diphtheria and poliomyelitis put together.

INCIDENCE

In 1940 the mortality rate per 100,000 population as reported for the entire United States registration area[27] was 2.7. There were 183,866 cases reported, giving a case rate of 151.6 per 100,000 population. In 1950 the mortality rate was 0.7, and the reported cases totaled 120,718. The increase in population following World War II resulted in the decrease in case rate to 59.3 per 100,000. In the next three year period the available figures from the National Office of Vital Statistics[28] showed that the mortality rate for the entire United States had dropped to 0.2 per 100,000. There has been a steady drop in the number of deaths under one year of age, but the highest figures are still seen in this group. The morbidity figures for 1953 have been determined by

Pittman[19] to be 37,129 reported cases with a case rate of 23.5 per 100,000.

Pittman[21] has evaluated the relative importance of pertussis in the field of communicable diseases as of 1955. The decline in both mortality and morbidity rates is shown, and the factors influencing this trend are thoroughly discussed. The persistence of the relatively high incidence of whooping cough and the fact that severe whooping cough in infancy is often a pediatric emergency requiring the most skillful handling on the part of physicians and hospital personnel justify a general discussion of the management of whooping cough.

CLINICAL PICTURE

The symptomatology of pertussis varies in intensity and duration in different age groups and may be influenced by the immune status of the person or by the administration of specific drug or serum therapy. A classic case of whooping cough in a susceptible middle-sized child follows a progressive pattern and can be divided into three stages. The *preparoxysmal* or *catarrhal stage* lasts seven to 14 days, or perhaps as long as 21 days. The first symptoms are those seen in any beginning upper respiratory disease. There is rhinorrhea and some nonproductive coughing. This may or may not be accompanied by a low grade fever. The child complains of no particular malaise. The cough, which is at first not remarkable, increases in intensity and frequency. At first it is present only during the day, then becomes aggravated by exercise, change in environmental temperature, and eating or drinking, and finally becomes nocturnal. The attacks of coughing become severe enough toward the end of this stage to cause suffusion of the face and, perhaps, vomiting.

The *paroxysmal stage* is the inevitable continuation of the primary symptoms, and it is at this time that the diagnostic characteristic of the cough appears. The inspiratory whoop, heard at the end of a long paroxysm of coughing, is usually followed by expulsion of a thick, tenacious amount of mucus which is present in the bronchial tree at this stage of the disease. Vomiting is common, and the patients become exhausted by the paroxysms. At the height of the paroxysms the face and neck become dark red or purplish, the eyes bulge, and the blood vessels are full and tense. In some instances there is mild to severe hemorrhage from the nose, pharynx and esophagus during attacks of coughing. Subconjunctival hemorrhages are common. There may be sudden unexplained convulsions and the development of central nervous system manifestations resembling those of encephalitis. There also may be a sudden rise in temperature with increase in the respiratory rate, chest pain and other signs of bronchopneumonia. This stage lasts for two to three weeks.

In the *stage of resolution* the severe symptomatology at first almost imperceptibly becomes less severe, and the final stage of regression or resolution becomes apparent as the condition progresses into one of paroxysmal coughing which is less severe in intensity and duration, accompanied by a decrease in the amount of vomiting. The old wives' tale describing "whooping cough three weeks coming, three weeks staying and three weeks going" is not too far wrong in untreated cases of this disease even now.

A variation of this classic picture is seen in small infants. The preparoxysmal stage progresses more rapidly, and many infants, particularly those in the very young age group, may not produce the characteristic whoop, probably because of their small chest structure and immature respiratory apparatus. These babies do not handle their paroxysms well and become cyanotic and even apneic during the paroxysms. They vomit more often than older children and seem to be more susceptible to changes in their environmental temperature and to hot and cold feedings. All these factors make it more difficult to plan the management of this disease in the younger age group.

The case of whooping cough seen by most clinicians who have at their command modern immunization facilities will be in a child who has a severe productive cough which may or may not be paroxysmal, and who often does not demonstrate the clinical diagnostic sign of whooping. This child has probably received partial immunization, and a specific diagnosis may be possible only by obtaining a positive culture of the etiological agent. The symptoms may have been present for as long as in the classic case, but the three stages may not be as easily delineated. He is, however, just as infectious as the child with the typical disease. Because of the difficulty in diagnosis, this mild, possibly subclinical case is a grave menace to the susceptible young infants with whom he may come in contact.

The typical *course* of whooping cough may be changed and the inevitable sequence of events halted by giving broad-spectrum antibiotics or specific serum early in the catarrhal stage of the disease. The symptoms may disappear three to four days after the start of therapy, and in most cases will not recur if the treatment has been adequate. In a few instances the original signs and symptoms may reappear 10 to 14 days after therapy has been discontinued. Repeat cultures at this time are usually negative. The explanation for this reactivation of the symptoms at this particular time interval and also the reactivation of whooping and vomiting with each new upper respiratory infection for as long as two years after the original illness is not clear. Whooping cough caused by *Bordetella pertussis*[13] (the new name for *Hemophilus pertussis* will appear in the seventh edition of Bergey's Manual) is the only clinical condition in which this characteristically happens.

DIFFERENTIAL DIAGNOSIS

In the early catarrhal stage of whooping cough there is absolutely no way to distinguish clinically between an impending case of whooping cough and an impending case of cough caused by one of many other different etiological agents. A disease clinically indistinguishable from classical whooping cough, but much less severe, is caused by the *Bordetella parapertussis*. *Hemophilus influenzae* may cause a cough which it is impossible to differentiate from the cough seen in the early and even well advanced catarrhal stage of pertussis. There may even be whooping. More rarely, *Hemophilus parainfluenzae* may cause paroxysmal coughing. Viral bronchitis or pneumonitis frequently causes severe paroxysmal coughing accompanied by vomiting or even whooping. The time element in all these diseases usually helps to make the diagnosis, because the clinical course of these diseases is a great deal shorter than that of whooping cough caused by *B. pertussis*.

In infants between three months and one year of age, particularly between three and six months of age, an organic condition must be considered in the differential diagnosis. In mucoviscidosis severe coughing, often paroxysmal, accompanied by vomiting is a common finding as the respiratory phase becomes symptomatically apparent. Since there is no early diagnostic test for whooping cough, specific laboratory diagnosis is invaluable in planning the therapeutic regimen for these critically ill infants.

COMPLICATIONS

Involvement of the lower respiratory tract with resulting bronchopneumonia or diffuse pneumonitis is the most frequent complication of whooping cough. Again the young infants are more prone to have this type of difficulty. The thick secretion produced in whooping cough is difficult to expel from the bronchial tree, even when the anatomical structures are well developed and the patient is strong enough to deal with the situation. In infants with immature chest structures as well as an unmaturated nerve supply, the cough reflex is not well disciplined. Chest excursion during respiration is not adequate enough to give sufficient expansion to produce the effort needed to expel the tenacious mucus. As a result, areas of atelectasis develop throughout the lung, areas which are then invaded by the various bacterial agents present in the respiratory passages. The added stress of diminished alveolar area as well as the toxicity of the pneumonic pathology is often too great for a debilitated patient or small infant. It is usual to find this complication in most of the infants who die from whooping cough. In older children the areas of atelectasis, if they persist, may be the basis for the future development of chronic lung disease such as bronchiectasis.

Nicholson[17] described the effect of pulmonary collapse in pertussis and concludes that it is a common feature, and that if re-expansion does not occur in nine months, it is not likely to do so and bronchiectasis will result.

Vomiting accompanies the paroxysms of coughing throughout the disease except during the early catarrhal and late stages of resolution. Loss of weight is common, and in weak children and infants signs of malnutrition may develop. Feeding techniques must be carefully considered in the management of this disease in order to prevent depletion of the patient's body mass, which will then result in metabolic imbalance.

In older children and adults massive hemorrhage may occur as the result of the exertion of severe paroxysms. Prompt emergency transfusion may be necessary to combat the shock resulting from the blood loss.

The most unpredictable and baffling complication is the sudden appearance of central nervous system symptoms. There is no correlation between the severity of the disease and appearance of neurological symptoms. A sudden convulsive seizure late in the catarrhal stage or, most commonly, after the paroxysmal stage has become established, is usually the first indication of brain involvement. The child may recover from a single convulsion or a series of convulsions, or may become comatose and exhibit the signs and symptoms of irreversible encephalitis. The picture is comparable with that found in encephalitis associated with other infectious diseases.

The gross findings at autopsy following sudden death in pertussis are congestion, edema and scattered petechiae. In reviewing the current literature one still does not find a full explanation of the mechanism of brain damage in whooping cough. It is postulated[2] that the encephalitis is probably due to the direct effect of a toxin from the organism. There is also probably damage to the vascular structures by the same agent. The role of anoxia is not known, but it is thought that this too is important.

Reports of less well defined neurological sequelae in even uncomplicated cases of whooping cough are beginning to appear. As attention is being drawn to the developmental aspect of our young patients, the causes of behavior problems and problems of physical and mental retardation are being investigated. Schnute[25] reported on mental retardation following postpertussis encephalitis. A discussion by Levy and Perry[12] of mental retardation caused by pertussis covers the wider implications of this question.

Prompt diagnosis and institution of adequate therapy are the only ways to prevent the complications which invariably influence the prognosis of the disease most unfavorably.

Recently there have been some observations of the effect of *B. pertussis* organisms on fetal brain tissue cells in culture.[9] There are generalized cytotoxic effects which may be reversed by the addition of specific antiserum. If this damage is caused by a toxin, which is known to be present in the structure of the organism, one wonders why human antiserum, in which there are no demonstrable antibodies against the toxin, seems to be so effective in restoring the damaged cells to their original state. Further work in this field is under way.

SPECIFIC DIAGNOSIS

Accurate bacteriological diagnosis of children and infants who in any way may be suspected of having pertussis is of utmost importance because of the ever-growing evidence that specific therapy is effective only if used early in the catarrhal stage. This is the time when there may be no symptomatic signs of true whooping cough. Routine culturing for pertussis is not done in many laboratories. There has been some hesitancy on the part of laboratory personnel in undertaking what they fear will be a complicated technique and which they believe to be usually unsuccessful. Many clinicians often have felt that the diagnosis could be made symptomatically in due time, and therefore minimized the importance of culturing. Anyone who deals with the therapy of diseases of bacteriological etiology must realize the importance of reliable bacteriological consultation, because this is vital to effective chemotherapy. If a few simple directions are followed, successful bacteriological diagnosis of respiratory diseases can be carried out in any laboratory.

The nasopharyngeal swab method of obtaining the secretion for culture, if properly carried out, is the method of choice.[4] The swab should be prepared from fine nichrome or stainless steel wire, 28 gauge, cut in 8-inch lengths. A loop is made at one end to act as a handle. The tip is dipped in collodion and carefully covered with absorbent cotton. Each swab should be carefully checked to be sure the cotton tip is secure. With a little practice uniformly finely wound swabs can be made so that the cotton completely covers the end of the wire. The swab must not be too cumbersome to be passed through the tiny pasasges of the nasopharynx of a newborn infant.

The technique of securing the culture is fairly simple. The baby or child should be placed on a table or bed with the head extended over the edge. It is wise to restrain the patient so that flailing arms and legs will not interfere with the maneuver. The swab is passed through the floor of the nose gently, and with an upward twist of the wrist led into the nasopharynx. The distance the cotton tip of the swab is advanced is roughly the distance from the tip of the nose to the tragus of the ear. The swab should be held in the nasopharynx for 30 to 60 seconds if possible. Coughing or choking during the procedure will result in a more satisfactory culture. The swab should be quickly removed and taken to the laboratory as soon as possible. If there is a delay between obtaining the culture and getting the specimen to the laboratory, it is wise to keep the specimen moist by having a piece of damp sterile cotton or cellulose sponge in the bottom of the tube. The pertussis organism is very sensitive to drying. In the laboratory the swab should be planted on fresh diagnostic media. The several bacteria

known to be etiological agents in respiratory disease have different growth requirements; therefore the appropriate media for the various organisms should be available.

The differential media for the common pathogens in the upper respiratory tract are nutrient blood agar, chocolate agar and Bordet-Gengou glycerin potato agar, a satisfactory medium for *B. pertussis*. This medium was used in the studies to be reported herein. There are several important points in the preparation and use of this medium which are necessary to bring about successful culturing. The culture base can be prepared in bulk, well sealed and stored for six months or longer. The formula as used in the laboratory of the Department of Pediatrics, University of Texas Medical Branch, is a modification of that recommended in the American Public Health Association's diagnostic procedure handbook.[7]

Peeled potato	200	gm.
Glycerin, C.P.	16	ml.
Bacto agar	48	gm.
NaCl	8.6	gm.
Distilled H_2O	1600	ml.
Nicotinic acid	20	mg./liter (=32 mg./1600 ml.)

Boil sliced potatoes in half the volume of water and glycerin until soft. Strain through 8 thicknesses of gauze. Make up to 800 ml. with additional distilled water. Add the salt, agar, nicotinic acid and remaining 800 ml. of water. Boil all this for a few minutes to dissolve the agar. Restore to volume of 1600 ml. with hot distilled water. Dispense 160 ml. per bottle. The bottles are autoclaved, sealed and stored. Pyrex nursing bottles are satisfactory for this purpose. For use, place a bottle of solid medium in boiling water to melt. Cool to 50° C. Add penicillin solution to make 0.2 unit per ml. of medium. Include the 30 ml. of blood that will be added. The blood should be freshly drawn, and under no consideration should be over one week old. Fresh horse or sheep blood may also be used. Pour 25 to 30 ml. per plate. Store plates in icebox. Do not use after 7 days, since they become too dry.

Commercial media have not always proved satisfactory in culturing for the pertussis organism. The Powell charcoal medium[23] gives good primary colony isolation, but in diagnostic work in which other pathogens are concerned is not as useful as the Bordet-Gengou medium. The *B. pertussis* colonies characteristically appear after 48 or 72 hours. They may not appear, however, for as long as five days. These colonies are small, translucent, gray, and pinpoint in size. The medium becomes dark beneath the colonies, and hemolysis is seen only when the colonies are well developed. To make a complete bacteriological diagnosis the original swab should be planted on rich, nutrient blood agar and chocolate agar plates as well as on plain nutrient agar. *Hemophilus influenzae* does not grow well on Bordet-Gengou medium. It may grow on blood agar, but its ideal medium is chocolate agar. It characteristically appears within 24 hours and can be differentiated from *B. pertussis* by the use of specific antiserum if there seems to be any question as to the identity. Pertusis organisms rarely grow on ordinary blood agar and never on plain agar. *Bordetella parapertussis* can grow on any of the three types of medium, but grows profusely on plain agar, causing some brown discoloration on the medium. Other pathogens, such as pneumococcus or Friedländer's bacillus, will not grow well on the Bordet-Gengou medium, but certainly will not grow at all if the medium is properly reinforced with penicillin.

If these procedures are followed, a bacteriologically minded clinician who has at his disposal a reliable laboratory with cooperative personnel will make early diagnoses and be able to treat his patients more efficiently and prevent the ravages of a potentially disabling illness.

The pertussis organism is present in the nasopharynx early in the catarrhal stage of the disease and in untreated cases may be recovered up to the sixth week of the disease. It is most frequently isolated, however, in the catarrhal and early paroxysmal stages. Careful culturing may yield positive results even when antibiotic therapy has been used.

Bordetella pertussis has not been definitely proved to be present in healthy carriers.

PREVENTION

Prophylaxis against pertussis has had a stormy history. Pertussis is included in the triple vaccine which has become routine in childhood immunization programs. The starting age and interval vary in different areas, but many physicians follow the recommendations of the American Academy of Pediatrics.[24] Three doses are given approximately one month apart, beginning at the second or third month of age. A fourth dose is recommended at one year of age. A preschool booster in addition to the primary immunization is probably sufficient to provide effective immunity. Whole bacteria vaccines in which the immunizing dose was based on total numbers of organisms vary greatly in potency.[22]

The vaccines are now prepared and standardized to meet the requirements of the U.S. Standard of Potency, which is expressed in protective units rather than numbers of organisms.[14] The regulations now limit upper level of protective unit content as well as the minimum lower level content.[15] The total immunizing dose is recommended to be 12 to 15 protective units.

Severe constitutional reactions following pertussis immunization, such as those described by Byers,[5] may be avoided by careful history taking before inoculations to rule out convulsive disorders or severe allergic reactions. Physical examination should be made to rule out impending or obvious respiratory infection or other illnesses which would contraindicate immunization with pertussis antigens. The unique characteristic of pertussis organisms to lower the histamine tolerance threshold in mice[18] may have some bearing on the occurrence of severe and even fatal reactions following any dose of an immunizing agent containing *B. pertussis*. Until more is known of the mechanism causing this complication, careful histories and physical examination before using the pertussis antigens are mandatory.

A noncellular pertussis antigen has been developed[10] which in preliminary trial as a single antigen appeared to be equally protective as the standard vaccines and to produce fewer local and general reactions. This material has been incorporated into a triple antigen and is now under clinical investigation. Another type of noncellular pertussis antigen has been developed[20] and is on trial in Great Britain. This product produces protection in mice, but does not produce agglutinins.[22] The noncellular antigen presently available may not be the ideal immunizing agent, but many investigators feel that efforts should be continued to produce a more refined immunizing agent which will be still more effective and produce even fewer reactions. In this way the continued

high incidence of this disease may be more satisfactorily decreased, and the babies and their doctors be spared the ordeal of severe pertussis.

TREATMENT

Many cures have been advocated for whooping cough over the years. A glance through the current literature gives references to such remedies as garlic phytoncides, high altitude flights, snail extracts, ACTH, fresh air and prolonged sleep, vitamins K and C, succinic acid, trypsin, hormones and antibiotics. In most instances the reports represent clinical impressions of the investigator. There are only a few studies in which significant results can be found. Because of the severity of this disease in young infants, some investigators hesitate to withhold treatment, so that the conventional rules of reliable clinical investigation are difficult to follow. The advent of specific antiserum[11] therapy gave the first promise of effective treatment, and continued use has established its value, particularly in infants with severe whooping cough. If the disease has advanced toward the paroxysmal stage, the addition of antiserum may be beneficial. In advanced cases one is forced to resort to the time-tried supportive measures to aid the patients to endure this long, exhausting experience.

In the detailed treatment of whooping cough, antibiotic therapy is the first consideration. With the advent of each new preparation has come a flood of hopeful literature. By and large the actual results have been disappointing in the over-all picture. Carefully controlled studies by Ames et al.[1] and the British Research Council[6] show that antibiotics, to be effective, must be used early in the catarrhal stage of the disease. Broad-spectrum antibiotic preparations such as chlortetracycline, Chloramphenicol, oxytetracycline, cathomycin and many others have been used with some success in early pertussis. Streptomycin is of questionable value. Newman et al.[16] have reviewed antibiotic therapy and conclude that intramuscular oxytetracycline is the therapy of choice in whooping cough. Steen and Rees[26] suggest that chlortetracycline (Aureomycin) used during the incubation period may protect exposed susceptible children from whooping cough.

Specific antiserum of high titer, both human and rabbit, is available in concentrated globulin type preparations. Two or three doses given *intramuscularly* reduce the severity of the symptoms. The use of human lyophilized or fresh hyperimmune serum given intravenously in doses of full serum tolerance (6 to 8 cc. per pound) daily until improvement is shown may be lifesaving in moribund infants.[3] The earlier in the disease any type of serum is used, the more effective it is. The administration of antiserum, as well as of antibiotics, is followed by prompt

disappearance of the organisms from the respiratory tract and regression of the lymphocytosis.

Supportive therapy is an important factor in the management of whooping cough, again, particularly, in the small infants. Sedative cough mixtures of all types are contraindicated because suppression of the cough reflex increases the possibility of atelectasis. An atmosphere of increased humidity with the addition of oxygen as needed is helpful. The addition of surface-wetting agents to the nebulized water is of quesionable value. Emetics have been of little value and in fact are contraindicated in most cases. Fluidifying agents such as trypsin used parenterally and by aerosol spray have not produced the expected results. Parenteral fluid therapy, including blood and plasma, is invaluable in critically ill patients.

DISCUSSION

A review of 343 cases of pertussis that have been under our care is the basis for emphasizing several aspects of the current therapy and prevention of pertussis. In a three year period during which an epidemiological study was carried out to evaluate a noncellular pertussis antigen, the staff of the Department of Pediatrics, University of Texas Medical Branch, was constantly aware of this disease. All patients attending the clinics who had even the remotest symptoms of pertussis were suspected of having pertussis until proved otherwise. Nasopharyngeal cultures and serial white and differential blood cell counts were done in as many cases as possible. Cultures were obtained from 239 children. One hundred seventy-eight, or 74.4 per cent, had positive cultures for *B. pertussis*. Of the 61 children with negative results, all but 14 had siblings who showed positive cultures. Records of white and differential blood cell counts were found in 145 cases. In general, there was fair correlation between the percentage of positive cultures and incidence of lymphocytosis in the children studied.[29] These results will be reported in another publication.

Several types of therapy were used during this three year period, and a review of the results in a group of patients treated with several therapeutic agents reflects the experience of other investigators who have reported that antibiotic therapy is disappointing in this disease. Because of the nature of the clinical study, and a high index of suspicion in the medical personnel, most of the cases mentioned here were seen early. The fair and poor results were invariably seen in patients referred late in the course of their disease. We are inclined to agree with the conclusions of the British workers[6] who feel that failure to observe ameloriation in whooping cough following antibiotic therapy might support a view that infection with *H. pertussis* sets in train a sequence of events

which, once started, is not greatly affected by elimination of the pathogen. Their study suggests that early recognition and early antibiotic therapy of whooping cough may help to reduce the severity of the infection, but that little is to be gained from antibiotic therapy if even slight symptoms have been present for more than a week.

In our study 48 patients ranging from one month to 14 years were treated with Chloromycetin,* 50 mg. per kilogram given for six days by the rectal route. The response was considered to be good in 70.8 per cent, fair in 25 per cent and poor in 4.2 per cent. During this same period 25 children were treated with antipertussis rabbit serum.* The dose required to produce good results was 2 to 3 ampules. One ampule in our experience was not always sufficient to produce lasting improvement. The results of this series were good in 72 per cent, fair in 16 per cent and poor in 12 per cent. A third group of children, 31 in number, were treated with an experimental antibiotic, Thiocymetin.† The material was given orally in a dosage of 40 mg. per kilogram daily for six days. The response was considered good in 64.5 per cent, fair in 32.2 per cent and poor in 3.3 per cent. No special attempt was made to evaluate the effect of hyperimmune human serum in the cases reported at this time. However, in all instances in which an infant in the study did not respond well to its assigned therapy, hyperimmune antipertussis human serum was included in the regimen. In all, 35 infants received this treatment, usually well along in their disease. In most cases some antibiotic therapy had already been instituted. It would be difficult to evaluate the effect of hyperimmune serum in this study because of the other variables involved. There was only one death in this group.

The addition of wetting agents to the humidifying apparatus generally recommended for use in severe pertussis in infants, and even older children, is of questionable value in our hands. Increase in humidity does appear to make the patients more comfortable. Oxygen is usually included in the setup.

SUMMARY

Whooping cough is still a disease of some importance in the pediatric age group. Early bacteriological diagnosis presents the only efficient method of cutting down the duration and severity of the symptoms, inasmuch as antibiotic therapy is helpful only in the preparoxysmal stage of the disease, at which time it is clinically impossible to diagnose this disease symptomatically. A suspicious mind and persistence on the part of clinicians in improving culture methods and in attempting bacteriological diagnosis seem to be the keys to future advances in the

* Supplied by courtesy of the Wyeth Company.
† Supplied by courtesy of Winthrop-Stearns.

therapy of this disease. Effective prophylaxis is the ultimate key to the eradication of whooping cough. Continual search for ideal immunizing agents will aid in reaching this goal.

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ALLERGIC PROBLEMS IN THE UPPER RESPIRATORY TRACT, INCLUDING THE EAR

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The upper respiratory tract is frequently the site of allergic reactions in children. These reactions are highly variable, especially as to the ease with which they may be recognized. In reviewing these clinical patterns it seems appropriate to emphasize the less typical manifestations.

WHEN TO SUSPECT ALLERGY

When chronic or recurrent upper respiratory difficulties are not accompanied by a typical allergic rhinitis, with its pale, wet, swollen nasal mucosa, and when there are no typical allergic difficulties in the patient's past or family, doubt normally exists as to whether allergy contributes to a process that seems predominantly infectious. It is often difficult or impossible for the physician to recognize the allergic element unless his level of suspicion of allergy is relatively high. On the other hand, allergic disposition to upper respiratory disorder may be suspected whenever a child seems to have more than a usual share of colds, or to have colds which last an unusually long time, particularly when the time of onset or duration corresponds to that of a seasonal allergen. Many children, for example, who have repeated or prolonged winter colds are allergic to house dust. By the same token, correspondence of symptoms to a particular time of day may suggest the allergic root of the patient's difficulty. Coughing or sneezing that occurs only in the night or only for a few hours after rising may result from exposure to specific allergens in the bedroom or from a relative increase

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in parasympathetic tone during sleep, which disposes to the emergence of symptoms at night in the allergic child.

The allergic element in respiratory disorders is further to be suspected when there seem to be unusually conspicuous *sensory* symptoms, such as an itchy nose leading to nose-rubbing (the "allergic salute") or excessive sneezing, or an itchy throat that leads to attempts to rub or scratch with the tongue or finger. A chronic, irritative, unproductive cough may depend upon analogous sensory disturbances in the larynx, trachea or bronchi.

A personal or family history of allergic manifestations sharpens suspicion, but the parents of the allergic child may have as obscure manifestations as he and be unaware of their own allergic respiratory problems. They cannot simply be asked whether they have manifest allergy, but must be questioned carefully as to the existence of symptoms of allergy masquerading as sinusitis or chronic bronchitis, either current or past.

Sometimes there are distinctive physical features in the allergic child with chronic or recurrent upper respiratory disorder. Recurrent or chronic periorbital edema or chronic mouth breathing may call attention to chronic allergic nasal obstruction and congestion. The related flattened malar eminences and broadened appearance of the root of the nose, with "circles" under the eyes, constitute the "allergic facies." Brown[1] pointed out that this is the same as the so-called adenoid facies, but that it results from reactive changes in the nose rather than from adenoid hypertrophy. A mucoid or mucopurulent nasal or postnasal discharge may also clearly locate the child's difficulty in the nose or sinuses rather than in the tonsils or adenoids. Excesses of lymphoid tissue are, nonetheless, common in the allergic child. He has a strong and such a unique tendency towards regrowth of such tissue after tonsillectomy or adenoidectomy that the observation of regrowth is almost pathognomonic of basic allergic constitution.[5]

Certain laboratory examinations may be helpful in diagnosis, but do not in any way take the place of careful and continuous clinical appraisal of the child. Eosinophilia in nasal secretion or aural discharge may indicate the allergic nature of reactive changes in the corresponding mucous membranes. When infection is superimposed, however, a neutrophilic exudate can be expected. Eosinophilia in the blood smear is in some measure corroborative of clinical suspicion of allergy, but absence of eosinophilia does not exclude it.

Skin tests may be helpful not only in pointing to specific allergens, but also in demonstrating an allergic type of reactivity to potentially allergenic material. Wide differences, however, exist in the intensity of skin reactivity in allergic children, and absence of typical responses does not exclude allergy, neither to the specific allergens tested nor as a basic contributory factor in the child's illness.

It seems unnecessary to review here the well known clinical manifestations of seasonal allergic rhinitis due to pollen (hay fever). Certain atypical manifestations of allergy in and about the upper respiratory tract, however, deserve further comment.

RHINITIS IN INFANCY DUE TO COW'S MILK

Clein[3] called attention to the occurrence of chronic rhinitis in infants of the age of only a few days or weeks who are allergic to cow's milk. We have seen several such infants. Gastrointestinal symptoms may coexist. The associated nasal obstruction may interfere greatly with respiration and with nursing. Relief is often dramatic when the offending food allergen (usually cow's milk) is removed from the diet.

We have not yet seen allergic rhinitis in the first year of life due to pollen reactivity, but such occurs from time to time.

CHRONIC AND RECURRENT RHINITIS AND SINUSITIS

A variety of names have been given to the tendency of many allergic children to have recurrent or chronic upper respiratory infections as the main or the sole manifestation of allergy. Depending upon the relative intensity of the apparent infectious or allergic or reactive elements, these children are said to suffer from perennial allergic rhinitis, recurrent upper respiratory infection, "sinusitis," vasomotor rhinitis, "the virus," "adenoids" or just plain "colds."

Some of the clinical manifestations of perennial allergic rhinitis and recurrent upper respiratory infection in allergic children have been given, and it has been pointed out that sensory symptoms may be particularly conspicuous. Abnormalities in the roentgenographic densities of the nasal sinuses are so regularly seen in these children that we are inclined to regard them simply as an expected part of the pattern. Simple thickening of the mucous membrane is the usual finding. Polypoid or purulent sinusitis is rare. The reactive and exudative processes in the nasal and sinus mucous membranes may extend into the lower respiratory tract, or similar changes may develop in the two areas simultaneously. Even without such extension, however, a productive or nonproductive, hacking or "sensory" cough may be a prominent feature of either perennial allergic rhinitis or allergic recurrent upper respiratory infection. It often resembles the cough of pertussis, even to the point of vomiting with paroxysms.

These forms of upper respiratory allergy are common in allergic children, and they may be expected to respond as readily as other allergic difficulties to adequate therapy. They do not, on the other hand, respond any more readily than more typical allergic disorders to inadequate management. The general principles of therapy are outlined later.

RECURRENT LARYNGITIS

A number of observers[5, 7] have called attention to the frequency with which recurrent laryngitis may be a manifestation of allergy. Allergic croup may resemble either spasmodic or nonspecific infectious croup; usually, laryngitis appears during the course of an otherwise undifferentiated upper respiratory infection, is mild to moderate in degree, and responds readily to vapor and other supportive therapy. Tracheotomy is rarely needed. In an allergic family recurrent laryngitis in a child is strongly suggestive of future asthma. It demands careful evaluation of the child and his environment from an allergic standpoint.

RELATION OF ALLERGY TO THE EAR IN CHILDREN

There is increasing evidence[8] that recurrent or chronic otitis externa often results from basically allergic eczematous changes in the auditory canal. Whenever external otitis is resistant to, or recurrent after, adequate local therapy, investigation should be made for a possible allergic basis.

The most common aural manifestations of allergy are *recurrent* and *chronic otitis media*, which result from the combination of infection in the upper respiratory tract and of basically allergic, as well as infective, reactive changes in the mucosa of the nasopharynx, eustachian tube and middle ear. The infective element often takes the forms of typical perennial allergic rhinitis or allergic recurrent upper respiratory infection. Brown[2] summarized an impressive body of opinion that adenoid hypertrophy has little to do with this variety of recurrent or chronic otitis media and that adenoidectomy should be strongly discouraged in favor of measures directed at control of reactive changes in the nose and sinuses. We agree, and believe, with Shambaugh[8] and others, that the chronic changes in the nose and sinuses are usually allergic in origin, and that there is usually a compelling need for allergic as well as antiinfective therapy if the process is to be controlled.

It is uncertain as to how frequently the picture of serous otitis media may originate in allergic changes in eustachian tube or middle ear. Derlacki and Shambaugh[4] found that such changes are commonly responsible, on the other hand, for failure of closure of a tympanic perforation, with protracted otorrhea. In either of these circumstances an aural discharge, whether obtained by aspiration of the middle ear in serous otitis or by swab in the case of perforation, may be particularly mucoid and may show prominent eosinophilia in a stained smear. There is every reason to believe that examination of aural fluids should more often include this cytological study, particularly when difficulties are chronic or recurrent.

SOME NOTES ON MANAGEMENT

In these disorders diagnosis and therapy often go hand in hand. It is our practice, for example, to initiate study with a therapeutic trial of protection against major potential inhalant allergens, such as house dust, feathers and wool. House dust, in particular, with pollen and molds, plays a preeminent role in the initiation and protraction of symptoms. Many adequate guides to house dust control are available, and the bedroom is the key spot for this activity.

Foods are of secondary importance, except in early infancy, but must at any age also be taken into account. We generally suggest that certain foods of high sensitizing potential, such as chocolate, eggs, nuts and the like, be excluded from the diet, whether or not the patient is skin-reactive to them, and that, in addition, any other foods giving positive skin reactions be avoided so long as symptoms persist, or at least until it can be determined that they are not responsible for such symptoms. Occasionally relief of symptoms of allergic tension or fatigue gives us a valuable clue that a significant food has been excluded from the diet. We are particularly suspicious of milk as a possible offender when there have been symptoms of gastrointestinal allergy in early infancy.

At times when these respiratory disorders are dominated by bacterial infection, as when purulent otitis media or rhinitis is present, antibiotic agents will be helpful when used against susceptible organisms. However, repeated use of antibiotic or any other chemotherapeutic agents is no substitute for allergic management, and is especially useless when not guided by adequate clinical appraisal or bacteriological study of the infectious process.

Not infrequently, even without therapy specifically directed at the infectious element, the antiallergic measures outlined will lead to prompt improvement in the child's condition which is confirmatory of the clinical impression of allergy and a first step in therapy. When such improvement is not seen, we carry out desensitization to house dust and to reactive pollens and molds (among the latter we test routinely only to Alternaria and Hormodendron). Our preference is for a dosage schedule intermediate between the high-dilution program advocated by Hansel[6] and the higher doses suggested by others. We find that most children respond well to weekly injection of 0.025 to 0.1 ml. of house dust extract diluted to 1:100,000 to 1:10,000; for a few this will be too much, and for a smaller number it will be too little. Comparable doses of pollen and mold extracts are used. We do not feel urged to increase the dose of extract to the point of tolerance, as has frequently been suggested, except, occasionally, in uncomplicated pollenosis. In this last instance superior results may depend upon the use of maximal doses.

In the chronic and recurrent disorders which are the subject of this

outline the role of idiosyncratic or truly allergic response to the infecting agent is uncertain. We have commonly included a stock bacterial vaccine in our program of desensitization, but have only occasionally seen convincing evidence of its usefulness. In a small number of children, all of whom received house dust concurrently, the administration of a bacterial vaccine precipitated repeatedly a typical infectious exacerbation of symptoms. Certain of them appeared to be able to tolerate the vaccine when the dose of house dust was made sufficiently low, at which point they gained relief of symptoms. Tuft[9] has suggested that it may be just as important to begin administration of a bacterial vaccine at high dilution, when such reactions are seen, as it is to give at high dilution any more typical allergen which gives a reaction. Tuft further suggests that the intracutaneous route be used when bacterial vaccines are given.

When improvement occurs as a result of desensitization, we do not increase any dose beyond the level at which symptoms are relieved. If symptoms are made worse by therapy, we expect that improvement will follow when we have substituted a lower, tolerated dose of allergen. When an intercurrent pollen season is responsible for relapse, we commonly combine coseasonal intracutaneous desensitization with perennial subcutaneous injections; in some children this seems dramatically efficacious.

If, in a child with possible or probable upper respiratory allergy, there is no change in symptoms after six to eight weeks of careful desensitization therapy, a complete review of the therapeutic program is in order, to establish (*a*) the adequacy of control of environment and diet, (*b*) the propriety of choice of material and dosage used for desensitization, and (*c*) the validity of the original diagnosis. An *adequate* therapeutic program usually begins to bring relief within six to eight weeks.

CONCLUSION

It is easy to say that if a program does not help in six to eight weeks, it is likely defective and should be reviewed. It is nearer the truth to say that the program should be under constant review, since it is manifestly impossible to present a diagnostic or therapeutic program for the allergic infant or child which will be universally applicable. Owing to the constitutional and environmental differences between children, one might expect only conjoined twins to present the same allergic problem.

Moreover, if the child and his problem are to be seen most clearly in relation to his environment, consideration of emotional and educational factors may be of prime importance. We believe that with treatment these allergic disorders have a good prognosis for normal development and activity; however, when parental anxiety takes the form of

overprotection, overdressing, underexercising and other forms of overrestriction of the child, this anxiety impedes optimal evolution of the child. We urge that these children be permitted to enjoy all tolerated activity appropriate to their ages, except in certain areas where prophylactic avoidance of sensitizing material may greatly safeguard the future—as in house dust control and in certain items of diet. In these areas restriction is often a nuisance, so far as the parent is concerned, and may be annoying to the child. Most parents and children, however, cheerfully accept limitations at home which do not interfere with reasonably normal social and educational activity outside the home, and many are able, with help and understanding, to come to grips with their allergic problems in ways which make the necessary restrictions and injections growth-promoting experiences.

SUMMARY

Atypical manifestations of allergy in and about the upper respiratory tract in children may include chronic and recurrent upper respiratory infections, recurrent laryngitis and chronic or recurrent otitis media. Clinical features and management of these conditions are briefly discussed.

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ASTHMA

Management of the Acute Attack and of the Chronic Disease

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It is perhaps unnecessary to state that before treating a child for asthma the diagnosis should be definitely established. In very young infants, particularly, this may present a real problem. For example, probably more than 25 per cent of the infants under one year of age referred to the Clinic for study with a diagnosis of bronchial asthma do not have this disease, but suffer from some form of congenital stridor. *The diagnosis of bronchial asthma is a clinical and not a laboratory diagnosis.*

Bronchial asthma is a serious disease, and its presence is always an indication for a complete study by a competent allergist, preferably, in the case of a child, one whose principal interest is infants and children. This discussion will be concerned only with the symptomatic treatment of bronchial asthma and, to a certain degree, with the prophylactic measures which should be implicit in this procedure. With this in mind the treatment of bronchial asthma in infancy and childhood, for purposes of discussion, may be conveniently divided into four categories: (1) prophylaxis of the acute attack, (2) treatment of the acute attack, (3) management of status asthmaticus and frequently recurring attacks of asthma, (4) management of the child with chronic asthma.

PROPHYLAXIS OF THE ACUTE ASTHMATIC ATTACK

In bronchial asthma, as in any other disease, the best treatment is prophylaxis. Previous studies[12] have shown that about 80 per cent of

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asthmatic attacks in children 10 years of age or less are preceded by definite and often constant prodromal symptoms which the parents recognize as indicating an impending attack. Asthma started suddenly in this series without prodromal symptoms in only about 20 per cent of the children. Though the interval between the onset of the prodromal symptoms and the onset of the asthmatic attack may, at times, be brief, in the 80 per cent of cases mentioned it varied from a significant fraction of an hour to several days. The prodromal symptoms are respiratory in about 90 per cent of the 80 per cent of children in whom prodromal symptoms occur. The most frequent symptoms are sneezing,

TABLE 28. *Instructions for the Prophylaxis of Asthmatic Attacks*

Name Date Age Height in.; Weight lbs.

I. *IMMEDIATELY* at the very first sign of an impending "cold" or asthmatic attack, which in this case is ....., proceed as follows in an attempt to prevent the condition from progressing and developing into asthma:

1. Put the child to bed in a room as free as possible from house dust, feathers, wool, animals of all kinds with fur or feathers, and free from odors, particularly fresh paint, tobacco smoke, burning leaves, cooking, etc.
2. The following medications are to be started *simultaneously* and repeated every 4 hours the first 24 hours when the child is awake and thereafter as may appear desirable:
   (a) An antihistamine:
   (b) Nose drops:
   (c) One teaspoonful of the cough mixture No.....

These medications must be started *as soon as possible*, since a delay of even an hour militates against the best results.

II. Insert an aminophylline suppository that night at bedtime and repeat every 12 hours thereafter until the danger of an asthmatic attack is passed.

III. If the above measures fail to prevent or minimize the "cold" or asthmatic attack, then with the next episode, along with Items (a), (b) and (c), an antibiotic should be given. This will be prescribed by your doctor or from this office.

nasal discharge and cough, commonly occurring in that order, before the onset of the asthma, although all may occur simultaneously. These symptoms are, of course, those of the onset of a coryza the origin of which is an infection or the expression of an allergic edema of the nasal mucous membranes. The nonrespiratory prodromes (which occur in about 10 per cent of the 80 per cent of children who have prodromes) are varied and bizarre and are, for most part, ocular. They may perhaps be explained by infectious or allergic edema of the conjunctivas. Tearing is the most common symptom, and the parents may describe the child's eyes as appearing glassy, staring, pale or peculiar.

The details of the prodromal symptoms are determined by a carefully taken history. The parents are then given detailed printed instructions as indicated in Table 28. They are asked to study these carefully, and the physician then goes over the directions in detail with the parents.

The antihistamine used is given in liquid form if the child is unable to swallow a tablet or a capsule. In this Clinic Benadryl is commonly used, for which a conservative dose is 2 mg. per pound per 24 hours.[24] The nose drop may be any vasoconstricting drop of the physician's choice. The cough medication should contain a cough depressant, a sympathomimetic drug, such as ephedrine, and an expectorant in a palatable vehicle.

It is important in the treatment of an asthmatic or any other allergic child that the parents learn the names of the drugs being used, and cough mixtures or any other preparations of multiple drugs should be given a number for purposes of identification. Then when the mother telephones the office for advice or comes in with the child, the medication may be easily identified from the record. In order for this to be possible, the pharmacist must be given proper directions for labelling on the prescription; otherwise the name of the preparation or its identifying number will not be indicated. Since pharmacists are not accustomed to doing this, these instructions are often disregarded, so that the parents must be directed to ask that the druggist carry out these directions if, through force of habit, he has not done so.

The following cough mixtures for a child about three years of age, which may be modified to suit the needs of the individual patient, have been found highly satisfactory:

Codeine phosphate (or sulfate)	0.25 gm.	(4 grains)
Ephedrine sulfate	0.40 gm.	(6 grains)
Glycerin	10.0 cc.	(2 drams)
Syrup hydriodic acid,		
*Syrup Cerasi N.F., āā q.s. ad	120.0	(4 ounces)

Label: Cough Mixture No. 1.
Sig: 1 tsp. q. 3–4 hrs. p.r.n. for cough.
(*If not available, use soda fountain syrup of cherry.)

If the patient is allergic to ephedrine, propadrine hydrochloride may often be used with success in the same or slightly larger doses. If the child is sensitive to codeine or other opium derivatives, Romilar Hydrobromide (Roche) may be used instead. This preparation, which is the dextrorotary form of 3-methoxy-N-methylmorphinan hydrobromide, is a non-narcotic cough depressant, 10 mg. (⅙ grain) of which are said to be approximately equivalent to 15 mg. (¼ grain) of codeine.

If syrup of cherry is not available, soda fountain syrup of cherry, which is essentially the same thing, may be substituted. This vehicle is accepted much more readily by children than the more commonly used syrup of wild cherry (Syrupus Pruni Virginianae).

Another satisfactory cough mixture for a child the same age is:

Dihydrocodeinone bitartrate	0.065 gm.	(1 grain)
Ephedrine sulfate	0.40 gm.	(6 grains)
Benylin expectorant, q.s. ad	120.0	(4 ounces)

Label: Cough mixture No. 2.
Sig: 1 tsp. q. 3–4 hrs. p.r.n. for cough.

The dose of dihydrocodeinone bitartrate (Hycodan) in adults is 5 mg. every four hours as necessary for cough; for children, in proportion to body weight. Any good antihistamine syrup may be used as a substitute for the Benylin expectorant.

For a more expectorant effect, without particularly changing the taste of the mixture, fluid extract of ipecac, 0.20 to 0.30 cc. (3 to 5 minims), may be added to either of the cough mixtures. *It must be remembered that the fluid extract of ipecac is about 16 times as active as the more commonly used syrup of ipecac.*

For nose drops, Neosynephrine 0.25 per cent is preferred. A buffered nose drop such as the Alcon-efrin No. 25 (Alcon Laboratories, Inc.) has been satisfactory and comparatively free from irritating effects. The drops should be instilled with the child in a semi-Proetz position; i.e., the child should be flat on his back with his head extended over the edge of the bed so that the nares and external auditory meatus are in a plane parallel to the floor. The drops should be given just before meals, so that if the child vomits after the medication, the meal will not be lost and also the child can breathe easier and therefore eat better at mealtimes.

Aminophylline suppositories should be used in a dose of 0.125 gm., 0.250 gm. or 0.500 gm., depending upon age and tolerance. Aminophylline may cause severe nausea, vomiting and abdominal pain on rectal administration. The danger attending the use of such suppositories has been stressed by Nolke.[27] The signal symptom which indicates that this preparation should be discontinued is almost always vomiting, particularly if persistent and progressive. If the suppository produces only local irritation, it may be lightly coated with an anesthetic ointment. For this purpose Tronothane Cream (Abbott) 1 per cent may be used, since avoidance of "caine" preparations in allergic children is desirable, although actually there appears to be little risk in their use in this age group.

If these measures are not sufficient to abort or satisfactorily modify the asthmatic attack, and particularly if the attacks are accompanied by fever, which commonly indicates infection, then an oral antibiotic should be used in addition to the previously mentioned medications. Penicillin is best avoided for reasons to be discussed subsequently. If it is necessary to use an antibiotic frequently, it should be varied in kind from time to time to avoid the development of resistant bacterial flora.

All the medications mentioned, except the anesthetic ointment and the antibiotics, are or contain agents which reduce edema, which is the fundamental abnormality of the physiology of the allergic reaction. The antihistamine neutralizes histamine, which acts on the minute blood vessels to cause edema; the sympathomimetic agents cause contraction of the smooth muscle of the blood vessel walls to prevent fluid from

passing through; and the aminophylline acts on the smooth muscles of the bronchi to cause relaxation and also, in some way not yet understood, as an antiedematous agent.

To be successful, the measures recommended must be used *immediately* at the very first prodromal symptom of the asthmatic attack. The longer the delay, the less the effectiveness.

If, in spite of these measures, the asthmatic attack is not aborted or satisfactorily modified, then it is reasonable to consider the addition of a sixth group of medications in addition to those previously used, namely, corticotropin or the corticosteroids. However, failures of this method of prophylaxis, if properly carried out, are so few that it is rarely necessary to resort to these drugs. It must be clearly understood that in the treatment of the ordinary attack of asthma such hormone therapy is not used as a primary routine measure, although it is possible that eventually this may become the treatment of choice.

TREATMENT OF THE ACUTE ASTHMATIC ATTACK

Though it is not always practical with older children, the child is preferably put to bed. This protects against aggravating factors, such as exercise and change of temperature. If the patient is potentially allergic or has had asthmatic attacks previously, environmental control should be instituted, at least in the bedroom. This should be as free as possible from house dust, wool, feathers and other epidermoids, pyrethrum-containing insecticides and from strong odors, as fresh paint, burning leaves, the dust from dried leaves, tobacco, tobacco smoke, cooking odors, perfume, kerosene, moth balls, fresh cut flowers, and so on. These are routine precautions which should be taken regardless of the history or skin tests.

If the asthmatic attack starts without prodromal symptoms, as occurs in about a fifth of the cases, or develops in spite of the above measures, the medications described above may be used symptomatically as indicated. Rarely, but sometimes surprisingly effectively, an asthmatic attack will respond to an antihistamine. The use of antihistamines, however, should not be continued if the attack persists, because of their drying effect. If the patient coughs, as is almost always the case, the cough medication should be used, and if the nose is obstructed, this should be relieved by the nose drops. Ephedrine by mouth in doses of 15 to 50 mg. (¼ to ¾ grain) (or some other sympathomimetic drug such as Propadrine or Isuprel) may then be tried. This reinforces the sympathomimetic drug in the cough mixture and may relieve the attack. Many tablets are available which contain a sympathomimetic drug, a sedative and a theophylline preparation such as aminophylline, and

these are popular for the oral symptomatic treatment of the acute attack.

If the patient is not relieved within 20 minutes by the oral medication, or if it has to be repeated oftener than every four hours, an aminophylline suppository should be given rectally, or, if the child will cooperate, the inhalation of epinephrine aerosol 1:100 is often most helpful. Children as young as three years may often be taught to use this procedure effectively. The child should always swallow or gargle with a little water after using to avoid pharyngitis and gastritis which may follow the use of epinephrine in this strength.

Occasionally an asthmatic attack may be checked by ipecac alone, a rather common procedure in folk medicine which has been particularly advocated by Ratner.[80] The drug is given to produce vomiting. This appears to relieve the attack in some instances by forcing mucus out of the bronchial tubes. The dose is 5 drops of the syrup of ipecac for infants one year of age or less, with one additional drop for each succeeding year. It is repeated every 15 minutes until the child vomits or until three or four doses have been given. The burning of "asthma powders" is also occasionally helpful, but it not now often used.

Steam inhalations may be useful in dry climate and in other climates in the winter when the air may be very dry. Steam is irritating to some children and in such cases should not be used. Medications, especially menthol, should not be added to the steam.

Epinephrine Injection

If the attack continues in spite of the above measures, recourse should be had without delay to the hypodermic administration of epinephrine 1:1000 as the quickest and most effective method of stopping the attack. It should be mandatory that someone in the family of an asthmatic child be able to carry out this procedure. Besides the obvious advantages for the child, the parents are usually impressed by the fact that if by this means even one house call by the physician is avoided, this will more than pay the cost of the hypodermic syringe, needles and medication.

The most common error in the use of epinephrine by injection is too long a delay between the onset of otherwise unrelieved asthma and the injection of the epinephrine. The parents should be told that *the earlier the hypodermic is administered, the more effective it is and the less the child will suffer.* It is also important that the epinephrine be administered in the proper dosage. The tendency is to use too large a dose. The proper dose is the smallest which will accomplish the desired effect, because this dose will also minimize the disagreeable side reactions. An infant four to six months of age may be started with 0.15 cc. (2 min-

ims). An average child of three years of age may be relieved by 0.20 to 0.25 cc. (3 to 3¾ minims). It may be necessary to repeat the dose several times at intervals of 15 to 20 minutes, gradually increasing the amount, if no result is obtained, until the child gets relief or shows the usual evidence of being refractory to the drug, as pallor, cold sweat, tremor, patchy cyanosis, nausea and vomiting. In the presence of fever, larger amounts are commonly necessary. Each patient with asthma is a law unto himself, and the parents soon learn how much to administer and how often. It is rare, indeed, that as much as 0.50 cc. (7½ minims) is required. If epinephrine is not well tolerated, ethylnorepinephrine (marketed by G. A. Breon & Co. as Bronkophrene) may be tried. The dosage is commonly twice that of epinephrine 1:1000.

As a substitute for epinephrine in oil, and often instead of the usual aqueous preparation of epinephrine, Sus-Phrine (Brewer), which is a 1:200 solution-suspension of epinephrine, has been found highly satisfactory. This is much simpler to administer than the ordinary epinephrine in oil, since it is an aqueous suspension which can be administered through an ordinary hypodermic needle. About 25 per cent of the epinephrine is said to be immediately available,[26] so that there is both an immediate and a delayed effect. Relief of asthma usually occurs in 10 to 20 minutes and lasts an average of six to 10 hours or more. The usual dose for children is 0.10 to 0.15 cc. (1.5 to 2.0 minims), depending upon the severity of the asthma and the presence or absence of fever.

When asthmatic attacks appear to be definitely associated with recurrent upper respiratory infections which have not responded to the usual methods of management, a determination of the blood level of gamma globulin is desirable. If this level, which is normally from 2.5 to 13 turbidity units (Kunkel)[23] according to Good and Zak,[14] is below normal, there is a definite indication to administer pooled gamma globulin intramuscularly. The dose recommended by Janeway and associates[21] is 0.10 gm. per kilogram of body weight once a month. It is not so commonly known that though the blood gamma globulin level may be normal or even high quantitatively, it may not be adequate qualitatively. This has been pointed out by Schick[32] and by Bowen.[3] Bowen obtained good results by the injection of 5 cc. of pooled gamma globulin every month. A limited personal experience appears to confirm Bowen's observations.

STATUS ASTHMATICUS

If the patient cannot obtain satisfactory relief from the asthmatic attack by the injection of epinephrine, he is then said, for purposes of discussion, to be "epinephrine-fast" and in "status asthmaticus." For-

tunately this is much less common in pediatric practice than in that of the internist, and since the advent of hormone therapy we rarely find it necessary to hospitalize a child because of status asthmaticus.

In status asthmaticus the drug which will give relief most rapidly is aminophylline injected intravenously. If helpful and tolerated, this may be continued as necessary until the patient responds to hormone therapy, which we institute almost routinely in status asthmaticus. The dose of aminophylline intravenously for adults is 0.25 to 0.50 gm., and for children in proportion to the body weight, administered slowly. Gastric distress, abdominal pain and severe vomiting may occasionally indicate intolerance for aminophylline, and if so its use should not be continued. We have never experienced serious reactions to this drug, as described by Nolke,[27] probably because its use has been discontinued if vomiting or other signs of disagreement occur.

The most common error in the treatment of status asthmaticus in childhood is *failure to keep the patient well hydrated*. This results in plugging of the smaller and sometimes the larger divisions of the bronchi with thick, inspissated mucus so that death may eventually result from suffocation. The bronchial secretions must be kept thin by plenty of fluid administered orally or parenterally. Other measures for keeping the secretions from thickening are steam (preferably cold, especially if the patient is in an oxygen tent), the use of expectorants and the avoidance of drying agents such as atropine and the antihistamines. We have had no experience with Alevaire (Winthrop).

One of the most commonly neglected of the expectorants in childhood is potassium iodide, which is used in a saturated aqueous solution given in fruit juice or water. The adult dose is 10 drops three times a day, preferably after meals. Children usually tolerate 5 drops without difficulty. If parenteral fluids are necessary, sodium iodide may be given intravenously in solution with the aminophylline. The adult dose is 1 gm., and children may be given this in proportion to the body weight. Fortunately, idiosyncrasy to iodine is rare in childhood. Oxygen is administered to children with severe dyspnea without waiting for cyanosis to develop, a symptom which occurs more frequently in this age group than in adults.

The child in status asthmaticus unable to tolerate fluids orally is hospitalized for intravenous fluid and drug therapy as described above. The patient is maintained on this therapy until corticotropin or corticosteroid therapy has taken effect. For this purpose, if the patient can tolerate oral medication, we now routinely give prednisone. So far as we can determine, the effects of prednisone, Nisolone and prednisolone are identical, and what is said here with respect to prednisone applies equally to prednisolone. This is in agreement with the work of Arbesman and Ehrenreich.[1] These drugs are used because they cause much

less disturbance of electrolytes than cortisone, hydrocortisone and corticotropin. If the attacks are severe, even in early infancy, and oral medication can be taken, the infant is started on 10 to 15 mg. of prednisone every six to eight hours for the first 24 hours. This is a larger dose than used by most, but we are firmly convinced that much time is saved and suffering avoided if a large initial dose is used. *There is no evidence that large doses of these hormones for short periods of time have any more deleterious effect than small doses over the same period.* If the patient gets relief, usually in six to eight hours, often before, the dose is reduced by 5 or 2.5 mg. per dose per 24 hours until the patient is on a maintenance dose of prednisone, aided by other anti-asthmatic medication short of the injection of epinephrine.

If the patient in status asthmaticus cannot take fluids by mouth, we now believe it advisable, although we have had but little experience with this method, to give hydrocortisone intravenously.[15] In the past the usual procedure was to make a solution of 100 mg. of the drug (supplied in ampules containing this amount) in 500 to 750 cc. of distilled water or 5 per cent dextrose and to give it, slowly, intravenously at the rate of 10 to 12 mg. (5 to 7.5 cc.) per hour. This proved to be highly disappointing, and because a much quicker response has been obtained by the intramuscular injection of hydrocortisone (see below) it is now our plan to administer hydrocortisone intravenously in smaller volume and more rapidly than indicated above. Doctor C. J. O'Donovan (Chief of the Department of Clinical Investigation, Upjohn Company) agreed and advised dissolving the hydrocortisone in 2 cc. of distilled water or normal saline solution and injecting it fairly rapidly over a minute or two. He stated that definitely better results have been obtained by this procedure than by the slow infusion method. The slower method was probably introduced because it is the custom to inject corticotropin very slowly intravenously. Entirely different principles, however, are involved in the intravenous injection of hydrocortisone, and there is no reason why it should not be injected rapidly. The medication may be repeated as indicated. As soon as the child is able to take medication by mouth the injection treatments are discontinued and prednisolone started orally.

Hydrocortisone is used for intramuscular injection if the child cannot take oral medication and intravenous injection is impractical. The recommended dose is a single injection every 24 hours of an amount which would constitute the daily dose were that preparation administered orally, i.e., 75 to 125 mg., depending upon the weight of the child and the severity of the attack. A preparation of prednisolone is now available for experimental study and, if it proves satisfactory for intravenous and intramuscular use, will probably become the treatment of choice, since it is less likely to upset electrolyte metabolism.

These procedures, if effective, are adaptable to home and office use and may make hospitalization for status asthmaticus unnecessary unless complicated by dehydration or infection.

The interval between the starting of the hormone therapy and the time it begins to take effect, usually one to several hours, may be a tense period, not only for the patient, but also for the physician. Ehrlich and associates[6] have recommended that during this interval intermittent positive pressure breathing of the type delivered by the Bennett or Emmerson machines be used and feel that this may be lifesaving. We have had, as yet, no experience with this procedure.

Hypokalemia

Corticotropin, hydrocortisone and cortisone all cause the body to lose potassium, and hypokalemia may develop. Though this condition occurs rarely, the possibility of its development should be kept in mind. The symptoms of potassium deficiency[5] are chiefly weakness, drowsiness, anorexia, nausea, chronic ileus with distention, edema, oliguria and shallow, infrequent respirations. It is easy to see how similar symptoms might also appear in an acutely ill infant or young child merely as the result of status asthmaticus per se. If it is suspected that hypokalemia is developing, the electrocradiogram, if it confirms the clinical findings, is probably a more delicate test than a determination of the blood potassium, which does not necessarily reflect the intracellular potassium.

Darrow[5] stated that when the concentration of potassium in the blood is between 3 and 4 mEq. per liter, the following electrocardiographic changes are likely to develop: slightly prolonged Q-T interval in relation to the P-T interval; decreased height and inversion of the T waves, and rounded, prolonged T waves and possibly inversion of the T waves, extra systoles and atrioventricular block. These changes are not specific, since they occur in other conditions. Their association with low serum potassium is evident when the changes disappear after serum potassium concentration has been restored to normal. Gibbs and associates[8] in a study of 48 infants ranging in age from two weeks to three years with potassium loss due to diarrhea felt that electrocardiographic studies offered a feasible and practical method of following potassium levels and thus can serve as a guide to management. They found changes in the T wave the most frequent of all abnormalities indicating hypokalemia and on the whole that the lowering of the T amplitude and the increased width of the T wave corresponded to the degree of hypokalemia. In the cases of dehydration with potassium loss the changes in the electrocardiogram were not as marked until the patient was hydrated.

If hypokalemia is suspected and the child can take fluids by mouth, the following prescription has been recommended by Randall and associates:[29]

Potassium acetate,	
Potassium bicarbonate,	
Potassium citrate, aa	15.0 gm. (½ ounce)
Water, q.s. ad	120.0 cc. (4 ounces)

Each teaspoonful (4.00 cc.) of this preparation contains about 14.7 mEq. of potassium. The dose for an adult (children in proportion to weight) is one teaspoonful three or four times a day in a flavored beverage. Potassium iodide is not satisfactory as a source of potassium, since the usual adult dose of 10 drops of the saturated solution supplies only 3 mEq. The use of citrous fruits is encouraged because of their relatively large potassium content. If it is necessary to give potassium intravenously, 0.2 per cent potassium chloride in distilled water may be given by slow drip. It is well to mention that potassium should not be given with impaired renal function or in severe dehydration.

How often one should take electrocardiograms for the study of potassium deficiency in status asthmaticus has not been determined. In one child in whom this condition was suspected and confirmed by the electrocardiogram these were made every two hours until recovery while the patient was receiving intravenous potassium.

Other Accessory Measures in Status Asthmaticus

Patients in status asthmaticus are routinely placed on a broad-spectrum antibiotic because the edematous lungs are easily infected and also because acute infection is a common precipitating factor in status asthmaticus. An antibiotic other than penicillin is preferable, as will be discussed subsequently.

Many patients in status asthmaticus, even children, require sedation. Our experience with barbiturates has not been highly successful. It has been helpful, however, in some patients who are unduly restless and apprehensive to give a small amount of Demerol with a little epinephrine (say 0.10 to 0.15 cc.) together in the same syringe. The epinephrine is not given to relieve the asthma under such circumstances, but merely to slow down the absorption of the Demerol, which will then exert its sedative effects, if used in the proper dosage, without the danger, in our experience, of respiratory depression which may attend the use of narcotics in the dosages usually given. The dose of Demerol in status asthmaticus is calculated according to the body weight (average adult dose 100 mg.), and only one half to one quarter of the calculated dose is given. The routine use of narcotics of any kind in status asthmaticus is to be deplored, and standing orders for narcotics, even Demerol, should never be written.

Maintenance Hormone Therapy

If a patient has almost continuous attacks of asthma which are not well controlled by any method of specific plus nonspecific therapy short of the injection of epinephrine, it is justifiable in the light of our present knowledge to keep the patient on maintenance doses of hormone. How long it is possible to do this without harm to the child is not known.

In one child who suffered with intractable asthma and did not respond well to any other form of therapy it was necessary to use maintenance doses of cortisone alternating at times with corticotropin for five years without apparent injury. One child with eczema who could be managed only with hormones and some local treatment made a spontaneous recovery in the course of a two year period. Hottinger[19] also described a child with allergy to cow's milk controlled by hormone therapy who made a gradual spontaneous recovery while under this treatment.

This suggests that maintenance doses of hormones will not interfere with spontaneous recovery from allergic disease, a comforting observation which awaits further confirmation.

The maintenance dose of hormone is determined as described for the treatment of status asthmaticus. It is advisable that a tuberculin test be performed before starting children on maintenance therapy, and, if positive, active tuberculosis must be ruled out.[13] The presence of tuberculosis is perhaps not an absolute contraindication to the use of hormone therapy if this is accompanied by the proper use of isoniazid and streptomycin as indicated by the reports of Houghton[20] and of Gregoire,[16] but until there has been more work done in this field, particularly with children, this cannot be recommended as a routine or danger-free procedure.

While the child is on maintenance hormone therapy the parent is instructed to report daily to the physician by telephone until the patient is under good control and to continue to report thereafter at intervals which depend upon how the child is getting along and the physician's evaluation of the intelligence with which the parents manage the problem. The basic principle is to reduce the dose to the smallest amount which will keep the patient under control, using other symptomatic therapy short of the injection of epinephrine. This tends to mitigate any possible ill effects from the hormone therapy as well as greatly to reduce the cost of treatment. We have had children do well on as little as 5 mg. of prednisone every second or third day. Some occasionally will require 10 mg. every eight hours for a week or more at a time. The dose will vary, depending upon exposure to various allergens as well as the presence of other stresses, particularly emotional disturbances such as unpleasant family situations, excitement attending birthday parties, and so forth. The patient is not put on a salt-free or low-salt diet because prednisone rarely causes significant disturbances of electrolyte

metabolism. However, it is requested that no more than customary amounts of salt be added to the food and that very salty foods as pretzels, salted peanuts, potato chips, ham, corned beef, herring, and the like, be omitted from the diet.

If there is any question regarding the ability of the parent to follow instructions, the child is put on concomitant doses of an antibiotic or sulfone drug in the same way as for prophylaxis of rheumatic fever.

When the maintenance dose is determined, this is interrupted at suitable intervals for the administration of corticotropin (ACTH) in such amounts that for each milligram of prednisone the patient empirically receives one unit of corticotropin. For example, if the maintenance dose of prednisone is 10 mg. per 24 hours, on the fifth day of treatment no prednisone is given, but the patient receives instead 40 units of corticotropin by intramuscular injection. In this way the depressing effect of prednisone on the adrenal cortex is believed to be neutralized by the stimulating effect of the corticotropin. Experimental and clinical support for this procedure is at present highly controversial, and it may eventually be shown to be completely unnecessary. However, in the light of our present knowledge no valid objection can be advanced, and certainly one feels more secure in the management of these patients when this procedure is practiced. While on hormone therapy the patient is weighed weekly at first, later every two or three weeks, the urine examined and the blood pressure taken. We no longer do eosinophil depression tests as a routine measure.

Forsham, for example (personal communication), is strongly of the opinion that it is not necessary or particularly desirable to give corticotropin in this manner, but states that he has never worked on this concept critically and has no data to support or deny it. He further feels that in the event corticotropin is given, the prednisone should not be discontinued that day.*

A complete discussion of the possible adverse effects of hormone therapy is beyond the scope of this article, but it is not out of place to mention the more important of them briefly. Moon facies occurs occasionally and is not a contraindication to the continuance of treatment, although one likes to avoid it if possible. Intercurrent infection, which may be masked, is perhaps the most dangerous complication. Tuberculosis has been mentioned. We have had many children get respiratory infections without interruption of hormone therapy or without protection of antibiotics because parents fail to report such infections.

The problem of corticotropin and corticosteroid therapy as related to some types of infection has been brought up to date by Robinson[30a] and by Jahn et al., [20a] who are essentially in agreement. Robinson states

* Essentially the same opinion was expressed in subsequent personal communications from Drs. N. B. Talbot, Paul Starr and J. W. Conn.

that although animal studies show that the corticosteroids may lower the resistance of a variety of animal species to many infectious agents, the reported incidence of intercurrent infections in human beings treated with adrenal cortical hormones appears to be relatively low. Jahn and his co-workers state that there is no evidence at present in the well nourished human being with a severe infection who is receiving antibiotics that hormonal therapy in any way interferes with antibody formation. These authors mention particularly that corticotropin or the corticosteroids should be used regularly in certain infections such as meningococcal meningitis, mumps orchitis and virus hepatitis. It is obvious from these and other studies that one cannot make a blanket statement that these drugs should not be used in the presence of infection. It all depends upon the infection and also, in some cases, on whether or not antibiotics or other anti-infectious agents can be used at the same time.

Haggerty and Eley[17] point out a greatly increased incidence of fatalities in children with chickenpox who have been receiving corticotropin or cortisone. One death was mentioned which occurred from encephalitis. Though two children attending this Clinic had chickenpox uneventfully while on hormone therapy, we now plan to give a large dose of pooled gamma globulin to those children who, in the future, have chickenpox under such circumstances. If one can judge by the work of Odessky and associates,[28] who used gamma globulin for the prophylaxis of measles encephalitis as soon as signs of central nervous system involvement appeared, the dose of pooled gamma globulin would be a total of 1.00 cc. per pound of body weight per 24 hours administered in divided doses. However, we plan to give the gamma globulin in our cases of chickenpox under hormone therapy as soon as the diagnosis is definite. There is some evidence that chickenpox may be attenuated by this procedure.[31] We shall also discontinue the hormone therapy in these circumstances.

Until now the development of a vaccine against chickenpox has not been assiduously pursued, perhaps because such a vaccine was thought to be of interest only from the experimental standpoint. However, in view of the findings of Haggerty and Eley, such a vaccine would now have great practical value.

Blodgett and associates[2] have reported that cortisone will usually slow the rate of statural growth and skeletal maturation within a week or two after therapy has been instituted. Of significance, however, is the sudden compensatory spurt in growth when the dosage is reduced or the drug eliminated, hypopituitary patients excluded. Hill[18] feels that if there is any retardation of growth in allergic children who are taking moderate or small amounts of cortisone, the retardation is not

great and is not sufficient to warrant withholding cortisone when needed. With this we fully agree.

Significant psychosomatic disturbances in children on hormone therapy have not been observed except improvement in mood as the clinical condition improved. Convulsions have been reported in a few cases in children following treatment with ACTH and cortisone, but this[7, 33] occurs rarely and cannot be seriously regarded as a contraindication. A number of our children on hormone therapy have suffered severe accidents and undergone major and minor operations without harm. Under such circumstances, however, doubling the dose of hormone is recommended if we know about the accident when it occurs or the projected operation.

Curtiss[4] reported one nine year-old boy with rheumatoid arthritis who had moon facies and buffalo hump while on hormone therapy. Osteoporosis was marked and multiple fractures occurred, but one can only surmise that the administration of the hormones was a main factor in this case. He also saw an eight year old girl who received large doses of cortisone as a lifesaving measure in an acquired hemolytic anemia who suffered multiple compression fractures in the dorsal spine.* However, I have seen no reports of osteoporosis and/or fracture in children with asthma under hormone therapy.

Ulcer with perforation has been reported in adults on hormone therapy, but has not been observed in children. If, however, a child complains of abdominal pain while on such therapy, we routinely administer an antacid.

MANAGEMENT OF THE CHILD WITH CHRONIC ASTHMA

Limitations of space compel only a brief discussion of this subject, which has been more fully discussed elsewhere.[10] However, an attempt will be made to cover the more important aspects of this subject. Since asthma is, generally speaking, a chronic disease, this discussion has particular reference to those children who have attacks more or less continuously or at least frequently enough to interfere with the usual activities of childhood. Happily, such problems are becoming gradually fewer as our knowledge of the specific treatment of asthma increases and particularly as we better understand the control of asthma, otherwise intractable, by maintenance hormone therapy. This has a parallel in the management of certain other diseases such as diabetes and hypothyroidism. Our ability to manage asthma in this manner is not without danger, since it is becoming fairly common practice not to subject allergic children to detailed study in competent hands, but to start immediately with the hormone therapy. This is a vicious practice, since in most instances asthma can be adequately managed by a competent allergist with only occasional help from the hormones, although

* Personal communication.

it must be admitted that there are still too many patients with asthma and other allergic diseases who now require maintenance therapy.

The environment of the asthmatic child should be as free as possible from allergens which have a high sensitization potential. These are, particularly, house dust and epidermoids. Other important allergens to be avoided, which also have a high sensitization potential, are cottonseed, flaxseed, kapok, India gum, orris, pyrethrum and silk. The child's bedroom should be designed to avoid these allergens, and specific directions for this purpose may be obtained from any allergist. They have also been published elsewhere.[11]

House dust is such a powerful and ubiquitous allergen that the entire house should be kept as free from dust as possible. This is a task of no mean magnitude. For houses heated by hot air the future holds great hopes for the universal application of the electrostatic precipitator, which has decreased each year in both the cost of installation and the size of the apparatus. Precipitators are now also available which are portable and may be moved from room to room, as desired. Such precipitators and air conditioners which filter out pollen and dust may also prevent, postpone or modify the development of pollenosis. The principle of electroprecipitation is now being combined with the ordinary room air-conditioning devices, now widely used for cooling in summer and filtration of pollen from the outside air.

The problem of animal pets is one of the most serious with which the pediatric allergist has to deal. Because children with asthma due to dog dander have been often encountered who, for example, did not react to dog hair and were not noticeably clinically sensitive to dog dander, it is our practice to ask that all animal pets be avoided. This is often exceedingly difficult to accomplish. At least, however, one can usually persuade the family to keep the animals out of doors and, if the pet dies, not to replace it. Our experience with pets as a cause of allergic disease has been such that we now advise the parents of a potentially allergic child (i.e., a child who has one or more allergic parents or siblings) not to acquire animal pets so that the child, if an allergic disease eventually develops, will not have to suffer the psychic trauma of losing the pet. Occasionally it is the parent, rather than the child, who demands that the pet be kept because of "psychological" reasons. This situation is commonly analogous to that of the young father who, when a son is born, purchases a miniature electric railway for the son's future use—only it is the father and not the son who gets the most fun out of the toy.

The child should sleep in a reasonably warm room, say 68° F. The pillow should be preferably of a plastic fiber (as vinyl or dacron) or of foam rubber and the mattress of foam rubber, although it is likely that

mattresses of plastic fibers will be developed which may be even more satisfactory than foam rubber. The sheets should be of cotton and the blankets of plastic material, and fuzzy bedding of any kind should be avoided.

The bedroom should also be free from strong odors of any kind, and pyrethrum-containing insecticides should not be used. Dusts of any kind may act as nonspecific irritants, and chalk dust in school is a not infrequent source of irritation. It is to be hoped that a newly designed chalk trough for schools which prevents the dust from getting out into the room will be widely adopted.* Paint is particularly important as a nonspecific offender, especially when it contains turpentine. There are now paints available reasonably free from odor, and whether these paints or any others are used, the child should not be exposed to the painted areas until the paint is dry and its odor has disappeared.

Outside clothing, regardless of current styles, should be adequate to protect against cold and dampness. Coarse woolens and furs and fuzzy materials are to be avoided.

It is highly important that the allergic child receive all protective immunizations, particularly tetanus, diphtheria and pertussis. The presence of asthma is not a contraindication to prophylactic injections. On the contrary, the need of such protection in the allergic child is greater than in other children because, if these diseases are contracted, there will be danger of reactions to the various serums and drugs which may be required for their treatment. In this connection it should be mentioned that bovine tetanus antitoxin[9] is available† for those who are sensitive to horse serum and have not been protected by tetanus toxoid. However, this may cause disagreeable reactions in children sensitive to beef or milk.

It is also important, particularly in allergic children, that the indiscriminate use of penicillin be avoided. Kern and Wimberly[22] stated that this antibiotic heads the list of medicinal agents in the frequency, diversity and severity of sensitivities which it induces, and it has replaced foreign serums as the commonest cause of anaphylactic shock. Though they had reference chiefly to adults, in whom drug reactions of all kinds occur much more frequently than in children, there is little doubt in my mind that the widespread and promiscuous use of penicillin, of which we, as pediatricians, have been unconsciously guilty, has probably sensitized untold numbers of children so that the internist-allergist for at least another generation will be adequately provided with patients. Penicillin should not be used if it is possible to use another antibiotic equally well; and if it is necessary to use penicillin,

* Tri-State Supply Co., 1750 West Fifth Ave., Columbus, Ohio.
† Merck, Sharp and Dohme.

it should be given orally if possible, since the evidence is that it is less likely to sensitize by this route. As the best general purpose antibiotic now available, penicillin should be used for those cases in which it is absolutely indicated rather than used at the risk of sensitization of the patient for an illness for which some other antibiotic might have proved satisfactory.

Although reactions to the penicillin in the Salk vaccine are doubtless exceedingly rare, the recent development of such a vaccine which does not contain penicillin* permits avoidance of the question of possible reactions to this drug in the immunization process. It is also felt that it makes good sense not to use penicillin in any preparation used for the routine immunization of children, however remote the dangers of sensitization from such a procedure may appear to be in the light of our present knowledge. An interesting comment on this has been offered by McLean.[25]

Practically every physician who treats asthmatic children is asked at one time or another whether or not a change of climate is advisable. This is often a disappointing therapeutic measure and should be undertaken only after all other measures for the study and treatment of the patient at home have failed. It is not without significance that many allergists always practice in those areas to which patients are usually sent because of the supposedly beneficial effects of the climate. Generally speaking, if the asthma is due to pollen, one may benefit for a time by a change of location, but sooner or later sensitivity to the pollen of the new location will usually develop. Persons who suffer asthma associated with cold may do better in warmer climates, and those who suffer from dampness may improve in less humid areas. But since such patients cannot leave their allergic constitutions behind, sensitivity to new or different allergens may develop wherever they may go. Many other factors are also involved, and for consideration of these, reference is made to a previous publication.[10a]

Lastly, since asthma is a chronic disease, generally speaking, and since the allergic constitution cannot be changed, one never knows when an allergic disease may recur in a given patient and what its effect may be upon his activities. For this reason it is important that one who suffers or has suffered from asthma should select a career in which, if the asthma recurs, it will not necessarily preclude the earning of a living. Employments to be avoided are those which involve considerable physical exertion, such as the teaching of physical education; exposure to animal danders and feathers, as farming and veterinary medicine; exposure to strong fumes, as in certain manufacturing processes; and occupations which involve exposure to damp, cold, and frequent changes of weather and temperature.

* Wyeth.

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INDEX

Page numbers of symposium and clinic titles are given in **boldface** type.

Abnormalities and deformities, association with respiratory tract anomalies, 96
of respiratory tract, **73–102**
Acetylsalicylic acid in nasopharyngeal infections, 156
Achondroplasia, 75
Acidosis, due to increased carbon dioxide tension, 7
metabolic, 8, 15
and respiratory alkalosis, 14
vs. pulmonary hyaline membrane syndrome, 15
respiratory, 8, 14
Adenovirus in etiology of pharyngoconjunctival fever, 120, 121, 122
Adrenocortical preparations, hydrocortisone, in croup, 179
in status asthmaticus, 301
Aerosols in bronchopulmonary disease, 237
Age, in prognosis of pulmonary tuberculosis, 259
influence on staphylococcal pneumonia and empyema, 218
Albamycin in nasopharyngeal infections, 164
Alevaire, effect in bronchiolitis, 188
Alkalosis, respiratory, and metabolic acidosis, 14
Allergic problems in upper respiratory tract, **285–91**. See also *Respiratory tract.*
Allergy, in croup, 172
relation to ear, 288
respiratory. See *Respiratory tract, allergic problems.*
Alveoli, dysplasia, congenital, 93
Aminophylline, in asthma, 296
in status asthmaticus, 300
Amniotic fluid, intrauterine aspiration, 33
Analgesics in nasopharyngeal infections, 156
Anencephaly, 75
Anoxia. See *Oxygen, deficiency.*
Antibiotics, broad-spectrum, in streptococcal infection, 147
Anticonvulsants in nasopharyngeal infections, 157
Antihistaminics in nasopharyngeal infections, 161
Antimicrobials, in bronchopulmonary diseases, 236, 238
in nasopharyngeal infections, 165
Antipyretics in nasopharyngeal infections, 156
Antiserum. See under *Blood, serum.*
Antitoxin in diphtheritic croup, 180
APC virus. See *Adenovirus.*
Apnea in newborn, 21
ARD virus. See *Adenovirus.*
Arteriovenous fistula, pulmonary, 94
Asphyxia pallida, 21
Aspiration, bronchoscopic, in bronchopulmonary disease, 240
Aspiration pneumonia in newborn, roentgen diagnosis, 35
Aspiration syndrome of postmatures, roentgen diagnosis, 33
Aspirin. See *Acetylsalicylic acid.*
Asthma, bronchial, acute, prophylaxis, 293
symptoms, 294
treatment, 297
chronic, treatment, 307

Asthma, bronchial, management of acute attack and of chronic disease, **293–312**
status asthmaticus, 299
treatment, accessory, 303
hormone, 304
Atelectasis. See *Lungs, collapse*.
Atmosphere control in prophylaxis of common cold, 110
Aureomycin. See *Chlortetracycline*.

Bacteria, in respiratory tract of newborn, 69, 70
pathogenetic, of respiratory tract of newborn, **69–72**
Bacteriological examination in bronchopulmonary disease, 233
Baths, sponge, in nasopharyngeal infections, 157
BCG. See under *Tuberculosis, vaccination*.
Benadryl. See *Diphenhydramine*.
Birth weight, hebdomedal deaths according to, 19
Blood, arterial, chemical changes in first 4 days, 10, 11
temporal, oxygen and hematocrit values, average, 11
buffer systems, 7
chemical deviations in respiratory disorders of immediate postnatal period, **3–16**
proteins, gamma globulin, in asthma, 299
in status asthmaticus complications, 306
serum, antiserum, in whooping cough, 279, 281
heterophile antibody absorption test, in infectious mononucleosis, 131
studies, in infectious mononucleosis, 130, 131
transport of carbon dioxide, 6
umbilical, chemical values, average, 9
Blood vessels, abnormalities, in newborn, 65
thoracic, normal, in newborn, roentgen findings, 30
Bone marrow in infectious mononucleosis, 128
Bordet-Gengou medium for bacteriological culture in whooping cough, 277
Branchial cleft cyst, 76
Breathing. See *Respiration*.
Bronchial cyst. See *Lungs, cyst, solitary*.
Bronchiolitis, **183–91**
acute, in newborn, roentgen diagnosis, 38
Bronchiolitis, clinical manifestations, 184
complications, 190
course, 190
differential diagnosis, 189
etiology, 183
infectious, vs. croup, 176
laboratory findings, 187
onset, age at, 185
pathology, 190
prognosis, 190
rectal temperature on admission to hospital, 186
roentgen findings, 186
treatment, 188
Bronchitis, asthmatic or capillary, acute. See *Bronchiolitis*.
Bronchobiliary fistula, congenital, 85
Bronchodilators in bronchopulmonary disease, 239
Bronchogenic cyst. See *Lungs, cyst, solitary*.
Bronchopleural fistula, congenital, 85
Bronchopulmonary suppurative disease, **231–41**. See also under *Lungs, diseases*.
Bronchoscopy, in bronchopulmonary disease, 233
in tuberculosis, 267
Bronkophrene. See *Ethylnorepinephrine*.
Bronchus(i), cleansing of, mechanical aids, 240
compression, 81
intrapulmonary, abnormalities, 85–95
major, abnormalities, 80–1
stenosis, 81
web, 81
Buffer systems in blood, 7

Carbomycin in bronchopulmonary disease, 237
Carbon dioxide, gas, in respiration, 4
tension, and hypoxia, increased, 12
decreased, 14
increased, in respiration, 4
transport, in blood, 6
Cathomycin in nasopharyngeal infections, 164
Cebocephaly, 75
Celomic cyst. See *Pericardial cyst*.
Cerebrospinal fluid in infectious mononucleosis, 132
Chemical factors in respiration, 4
Chemical regulation of respiration in neonatal period, 9
Chloramphenicol, in bronchopulmonary disease, 237, 238
in interstitial plasma cell pneumonia, 211, 212
in nasopharyngeal infections, 165

Chloramphenicol, in staphylococcal pneumonia and empyema, 225
in whooping cough, 281
Chloromycetin. See *Chloramphenicol.*
Chlortetracycline, in croup, 179
in interstitial plasma cell pneumonia, 211, 212
Choanae, atresia or stenosis, 75
Chonechondrosternon. See *Thorax, funnel chest.*
Cold, common, **103–13**
complications, 109
epidemiology, 105
etiology, 104
immunity, 108
incidence, 105
prophylaxis, 110
symptoms, 103
treatment, 109
Cold vaccines, 110
Conjunctivitis vs. pharyngoconjunctival fever, 126
Convulsions in whooping cough, 275
Corticotropin in status asthmaticus, 305
Cough, treatment in nasopharyngeal infections, 160
vs. whooping cough, 274
Cough mixtures in asthma, 295
Coxsackie virus, group A, 115, 116
infections, epidemiology, 116
etiology, 116
Cricoarytenoid joint, dislocation, 78
Cricothyroid joint, dislocation, 78
Croup, diphtheritic, 170
clinical manifestations, 173
complications, 176
pathology, 172
Hemophilus influenzae, 170
clinical manifestations, 174
complications, 176
pathology, 172
infectious, 169–82
allergy in, 172
bacteriological findings, 171
clinical course, 173
complications, 176
differential diagnosis, 176
etiological types, differential diagnosis, 180
etiology, 170
localization, 169
pathology, 172
treatment, 177
nonbacterial. See *Croup, virus.*
spasmodic, 175
virus, 171
clinical manifestations, 175
Croup, virus, complications, 177
pathology, 173
Cyanosis in newborn, 20
Cyclopia, 75
Cyst. See under specific organ or region.
Cytomegalic inclusion disease, roentgen diagnosis, 39

Deaths, hebdomedal, according to birth weight and respiratory group, 19
Demerol. See *Meperidine.*
Dermoid cysts, 83
Diaphragm, abnormalities, 95–6
accessory. See *Diaphragm, duplication, partial.*
duplication, partial, 96
eventration, 95
in newborn, roentgen diagnosis, 45
hernia. See *Hernia, diaphragmatic.*
paralysis, in newborn, roentgen diagnosis, 45
Dihydrostreptomycin in nasopharyngeal infections, 163
Diphenhydramine, in asthma, 295
in nasopharyngeal infections, 161
Diphtheria, 140
Distemper, canine, relationship to human respiratory disease, **193–201**. See also *Pneumonitis, primary.*
relation to measles, 199
Dornase, pancreatic, in bronchopulmonary disease, 239
Drainage, in complications of staphylococcal pneumonia, 226, 227
postural, in bronchopulmonary disease, 240
in nasopharyngeal infections, 159
Dust extract, house, in respiratory allergy, 289
Dyspnea, in newborn, 23
laryngeal, obstructive, 79
congenital, 78

Ear, relation of allergy to, 288
Ear drops in nasopharyngeal infections, 160
Electrocardiogram. See *Heart, electrocardiography.*
Emphysema, congenital. See *Emphysema, obstructive, lobar.*
hypertrophic, congenital, 92
localized. See *Emphysema, obstructive, lobar.*
lobar, in newborn, 64
clinical manifestations, 65
mediastinal. See *Pneumonediastinum.*

Emphysema, obstructive, lobar, 91
in newborn, roentgen diagnosis, 41
Empyema, in staphylococcal pneumonia, 222
staphylococcal, and pneumonia, **215–29**. See also *Pneumonia*.
Encephalocele, nasal, 76
Environment as factor in incidence of common cold, 105
Enzymes in bronchopulmonary disease, 239
Ephedrine in asthma, 297
Epiglottis, abnormalities, 78–80
in newborn, 67
bifid, 78
elongate, 78
Epinephrine, in asthma, 298
in status asthmaticus, 303
Erythromycin, in bronchopulmonary disease, 237, 238
in nasopharyngeal infections, 164
Esophagus, atresia, 84
roentgen diagnosis, 35
with tracheo-esophageal fistula, in newborn, 66
Ethylnorepinephrine in asthma, 299

FACIES, allergic, 286
Family background in prognosis of tuberculosis, 259
Fever, glandular. See *Mononucleosis, infectious.*
three-day, 119
Fistula, arteriovenous, pulmonary, 94
tracheo-esophageal, 83–5
Funnel chest. See under *Thorax*.

GAMMA globulin. See under *Blood, proteins.*
Gantrisin. See *Sulfisoxazole*, under *Sulfonamides.*
Gargles in nasopharyngeal infections, 159
Gases, respiratory, transport of, 6
Gastrointestinal tract, duplications, 83
in infectious mononucleosis, 128
Gingivostomatitis, infectious, vs. herpangina, 119
Glandular fever. See *Mononucleosis, infectious.*
Glioma, nasal, 76
Globulin, gamma. See under *Blood, proteins.*
Glomerulonephritis, and rheumatic fever, prevention, 147
epidemiology, 151
prevention, 151

HAMARTOMA of lung, 93
Harelip, 77
Heart, abnormalities, in newborn, 65
electrocardiography, in hypokalemia, 302
in infectious mononucleosis, 132
normal, in newborn, roentgen findings, 31
Hemangioma, laryngeal, 79
Hemoglobin, fetal, 6
in transport of oxygen in blood, 6
Henderson-Hasselbalch equation, 7
Hepatitis, infectious, vs. infectious mononucleosis, 133
Hernia, diaphragmatic, 95
congenital, in newborn, roentgen diagnosis, 43
in newborn, 66
Herpangina. See under *Throat, infections.*
Herpes simplex vs. streptococcal infection, 144
History in diagnosis of bronchopulmonary diseases, 231
Hormones in status asthmaticus, 304, 305
Host factors, affecting prognosis in tuberculosis, 259
in incidence of common cold, 105
House dog disease, 194
House dust extract in respiratory allergy, 289
Hyaline membranes, 12, 13
in newborn, 59
clinical manifestations, 60
etiology, 61
pathological findings, 60
roentgen diagnosis, 32
Hydrocarbon pneumonitis, **243–53**. See also under *Pneumonitis.*
Hydrocarbon products, ingestion of, morbidity, 249
Hydrocortisone. See under *Adrenocortical preparations.*
Hydrogen ion concentration, increased, in respiration, 4
Hygroma, cystic, 83
Hyperpnea, 5
Hypertelorism, 75
Hyperventilation, 4
Hypokalemia in status asthmaticus, 302
Hypoventilation in newborn, 12
Hypoxia, and increased carbon dioxide tension, 12
treatment, 14
in newborn, 58

IMMUNIZATION in bronchopulmonary disease, 240

Infection, intercurrent, in prognosis of tuberculosis, 260
treatment, in bronchopulmonary disease, 236
tuberculous, age of, in prognosis of primary lesion, 260
Influenza vs. pharyngoconjunctival fever, 125
Intra-alveolar hemorrhage. See under *Lungs, hemorrhage.*
Intraventricular hemorrhage in newborn, 55
etiology, 56
pathological findings, 56
Ipecac in asthma, 298
Isoniazid in tuberculosis, 265, 266
Isuprel in bronchopulmonary disease, 240

JAW, lower, abnormalities, in newborn, 67
Jellies, nasal, in nasopharyngeal infections, 159

KARTAGENER'S syndrome or triad, 93

LARYNGITIS, 170
recurrent, 288
Laryngocele, 79
Laryngomalacia, 78
Laryngotracheitis, 170
Laryngotracheobronchitis, 170
Laryngotracheobronchopneumonitis, 170
Larynx, abnormalities, 78–80
in newborn, 67
and laryngotracheal area, diseases, inflammatory, acute, **169–82**
atresia, congenital, 78
cyst, 79
dyspnea, obstructive, causes of, 79
hemangioma, 79
obstruction, vs. bronchiolitis, 189
stenosis, 79
stridor, congenital, in newborn, roentgen diagnosis, 47
web, 79
Lavage, gastric, in hydrocarbon pneumonitis, 252
Leukocytes, count, in streptococcal infection, 145
Lipiodol test in fibrocystic disease of pancreas, 235
technique, 236
Lissencephaly, 75
Liver function tests in infectious mononucleosis, 131
Lozenges in nasopharyngeal infections, 159

Lungs, abnormalities, 85–95
adenomatoid, congenital. See *Lungs, dysplasia, adenomatous.*
cystic, congenital, roentgen diagnosis, 42
cystic, 88
congenital, in newborn, roentgen diagnosis, 42
treatment, 90
agenesis, 86
in newborn, 64
in newborn, roentgen diagnosis, 46
aneurysm, arteriovenous, 94, 95
collapse, as cause of neonatal death, 54
cysts, postinfectious, roentgen diagnosis, 37
solitary, 82, 88
roentgen diagnosis, 42
diseases, bronchopulmonary, suppurative, **231–41**
etiological classification, 232
roentgen findings, 233
treatment, 236
cystic, diffuse, 89
fibrocystic, bilateral, diffuse, 89
in newborn, roentgen diagnosis, **27–52**
multicystic, 89
roentgen diagnosis, 42
dysplasia, adenomatous, 92
hamartoma, 93
chondromatous, 94
hemorrhage, intra-alveolar, in newborn, 64
honeycomb, 89
hyaline membrane. See *Hyaline membranes.*
hypoplasia, 87
in newborn, 64
lobation, anomalous, 86
lobe, agenesis, 87
azygos, 86
lymphangiectasis, cystic, diffuse, 90
normal, in newborn, roentgen findings, 29
sequestration, extralobar, 91
treatment, 92
intralobar, 90
treatment, 91
tracheal, 81
ventilation, in acidosis, 7
Lymph nodes in infectious mononucleosis, 127
Lymphocytes in infectious mononucleosis, 130

MANDIBULOFACIAL dysostosis, 75
Marrow, bone. See *Bone marrow.*

Measles, relation to canine distemper, 199
Mediastinum, cysts, 81–3
frequency, 82
Meningocele, anterior, 83
Mental hygiene in bronchopulmonary disease, 240
Meperidine in status asthmaticus, 303
Mesothelial cyst. See *Pericardial cyst*.
Metabolism, cerebral, 8
Milk, cow's, rhinitis due to, 287
Mononucleosis, infectious, 126–33
clinical manifestations, 129
differential diagnosis, 132
etiology, 127
laboratory data, 130
pathogenesis, 127
pathology, 127
prognosis, 132
treatment, 133
vs. streptococcal infection, 144
Mouth of newborn, bacteria in, 69
Mucoviscidosis. See *Pancreas, disease, fibrocystic*.
Muscle tone, relation to hypoxemia, 24
Mycobacteria, factors relating to, in prognosis of tuberculosis, 261

NASAL. See *Nose*.
Nasopharyngitis, acute. See *Cold, common*.
Nasopharynx, abnormalities, 76
infections, bacterial, **139–54**
nonbacterial, **115–38**
unidentified, **103–13**. See also *Cold, common*.
streptococcal, 141
symptomatic relief, **155–67**
treatment, antimicrobial, 161
agents, 162
route of administration, 162
symptomatic and supportive, 156
secretions, bacteria in, 184
swab method of bacteriological culture in whooping cough, 276
Neck, orangoutang, 80
Neomycin in bronchopulmonary disease, 137, 238, 239
Neo-Synephrine. See *Phenylephrine*.
Nerve, phrenic, paralysis, in newborn, 65
Nervous system, central, complications of whooping cough, 275
congenital malformations, 59
in infectious mononucleosis, 128
Neurenteric canal cysts, 82
Neurofibroma, nasopharyngeal, 76
Newborn, pulmonary disease, roentgen diagnosis, **27–52**
Newborn, respiratory disorders, correlation of clinical and pathological observations, **53–68**
respiratory function in, clinical evaluation, **17–26**
respiratory tract, bacterial pathogens of, **69–72**
Nose, abnormalities, 75–7
jellies, in nasopharyngeal infections, 159
obstruction, symptomatic and supportive care, 158
of newborn, bacteria in, 69, 70
passages, abnormalities, 75–6
septum, deviation of, 76
Nose drops, antibacterial, in nasopharyngeal infections, 159
in asthma, 296
Novex in interstitial plasma cell pneumonia, 212
Novobiocin in nasopharyngeal infections, 164
Nutrition, in prognosis of tuberculosis, 260
in tuberculosis, 267

ORANGOUTANG neck, 80
Otitis externa, chronic, 288
Otitis media, 288
Oxygen, deficiency, fetal, in newborn, 57
clinical manifestations, 58
pathological findings, 58
in premature infants, 11
Oxygen tension, decreased, in respiration, 5
Oxygen therapy, in interstitial plasma cell pneumonia, 211
in respiratory insufficiency in newborn, 25

PALATE, abnormalities, 77–8
cleft, 77
Pancreas, disease, fibrocystic, 231 *ff*.
in newborn, roentgen diagnosis, 38
Para-aminosalicylic acid in tuberculosis, 265, 266
PAS. See *Para-aminosalicylic acid*.
Paregoric in cough therapy, 161
Paul-Bunnell test in infectious mononucleosis, 132
Pectus excavatum. See *Thorax, funnel chest*.
Penicillin, in bronchopulmonary disease, 237, 238
in croup, 178
in diphtheria, 140
in glomerulonephritis, prophylaxis, 152

Penicillin, in nasopharyngeal infections, 162
duration of therapy, 163
in rheumatic fever, prophylaxis, 149, 150
in staphylococcal pneumonia and empyema, 225
in streptococcal infection, 146, 147
Pericardial cysts, 83
Pertussis. See *Whooping cough*.
Pharyngitis, exudative, nonbacterial, vs. streptococcal infection, 144
febrile, 119
streptococcal, 141
vs. pharyngoconjunctival fever, 125
Pharyngoconjunctival fever, 120–6
clinical manifestations, 123
complications, 124
differential diagnosis, 125
epidemiology, 125
etiology, 121
prognosis, 124
treatment, 124
Phenylephrine in asthma, 296
Phrenic nerve paralysis in newborn, 65
clinical manifestations, 66
Physical examination in bronchopulmonary disease, 232
Pierre-Robin syndrome, 78
Pleura, diseases, in newborn, roentgen diagnosis, 39
effusion, in newborn, roentgen diagnosis, 40
in staphylococcal pneumonia, 222
Pneumatocele, pulmonary, in staphylococcal pneumonia, 223
Pneumomediastinum in newborn, 63
pathological findings, 64
roentgen diagnosis, 39
Pneumonia, and empyema, staphylococcal, complications, 228
aspiration, in newborn, roentgen diagnosis, 35
giant cell, in newborn, roentgen diagnosis, 39
in newborn, 61
clinical manifestations, 62
pathological findings, 63
roentgen diagnosis, 34
plasma cell, interstitial, **203–14**
clinical manifestations, 207
complications, 210
laboratory findings, 209
mortality, 210
pathological anatomy, 205
prevention, 211
roentgen diagnosis, 39, 208
treatment, 211
Pneumonia, staphylococcal, and empyema, **215–29**
clinical manifestations, 220
diagnosis, 223
incidence, 217
influence of age on, 218
pathogenesis, 216
pathology, 216
prognosis, 228
roentgen findings, 221
treatment, medical, 224
surgical, 226
in newborn, roentgen diagnosis, 37
unusual types, in newborn, roentgen diagnosis, 39
Pneumonitis, hydrocarbon, **243–53**
clinical manifestations, 243, 248
clinical studies, material and methods, 246
results, 247
laboratory findings, 249
mortality, 244
pathogenesis, experimental studies, 244
roentgen findings, 244, 246, 248, 250
symptoms, 246
treatment, 252
interstitial, of newborn, clinical manifestations, 194
roentgen diagnosis, 39
primary, immunology, 198
pathology, 195
Pneumothorax in newborn, 63
pathological findings, 64
roentgen diagnosis, 39
Polymixin in bronchopulmonary disease, 237, 238
Postmatures, aspiration syndrome of, roentgen diagnosis, 33
Potassium in hypokalemia, 303
Potassium iodide in status asthmaticus, 300
Prednisone in status asthmaticus, 301, 304
Premature infant, blood chemical changes, 10, 11
Prematurity as cause of neonatal death, 54
Pulmonary. See *Lungs*.
Pyopneumothorax in staphylococcal pneumonia, 222
Pyribenzamine in nasopharyngeal infections, 161
Pyridoxine in tuberculosis, 266

Race in prognosis of tuberculosis, 259
Rash in scarlet fever, 142

Respiration, chemical deviations, 11
chemical factors, 4
chemical regulation, in neonatal period, 9
Cheyne-Stokes, in premature infants, 11
disorders of, in newborn, causes, 55
correlation of clinical and pathological observations, 53–68
treatment, 25
in newborn, roentgen changes during, 30
process of, 3
rate, fluctuations in, 18
causes, 23
in newborn, significance, 18
measurement, 25
recording, 25
regulation by carbon dioxide gas, 4
rhythms, in newborn, 24
seesaw, 23
tissue, 8
Respiratory alkalosis, 8, 14
Respiratory center, 3, 4
Respiratory function, clinical evaluation, in newborn infants, 17–26
Respiratory gases, transport of, 6
Respiratory group, hebdomedal deaths according to, 19
Respiratory reflexes, 5
Respiratory tract, abnormalities, 73–102
association with other anomalies, 96
clinical significance, 73
congenital, roentgen diagnosis, 41
frequency, 74
genetic aspects and implications, 97
incidence, 74
allergic problems, laboratory findings, 286
symptoms, 286
diseases, relation of canine distemper to, 193–201. See also *Pneumonitis, primary.*
relation to tonsillectomy, 111
symposium on, 1–312
disorders, blood chemical deviations in immediate postnatal period, 3–16
in infectious mononucleosis, 128
infections, diagnosis, 155
treatment, 155
of newborn, bacterial pathogens of, 69–72
upper, allergic problems in, 285–91
treatment, 289
Rest in tuberculosis, 267
Retropharyngeal space, normal, in newborn, roentgen findings, 31
Rheumatic fever, and glomerulonephritis, prevention, 147
clinical manifestations, 149
epidemiology, 148
prevention, 148
treatment, 149
Rhinitis, 287
Rhinodymia, 75
Rhinoencephalocele. See *Encephalocele, nasal.*
RI virus. See *Adenovirus.*
Ringer's solution, postoperative, in infectious croup, 179
Roentgen diagnosis of pulmonary disease of newborn, 27–52
technical considerations, 28

Salicylate intoxication vs. infectious croup, 176
Saline solutions in nasopharyngeal infections, 158
Salute, allergic, 286
Scarlet fever, rash of, 142
Sedatives in nasopharyngeal infections, 157
Serum. See under *Blood.*
Sinuses, nasal, abnormalities, 76–7
Sinusitis, chronic and recurrent, 287
Skin tests, in bronchopulmonary disease, 233
in respiratory allergy, 286
Sodium iodide in status asthmaticus, 300
Sodium phenobarbital in infectious croup, 178
Spleen in infectious mononucleosis, 128
Staphylococcus, in respiratory tract of newborn, 70, 71
pneumonia due to, in newborn, roentgen diagnosis, 37
Status asthmaticus. See under *Asthma.*
Steroids in tuberculosis, 267
Strawberry tongue in streptococcal infection, 142
Streptococcus, infection by, 141–7
differential diagnosis, 144
incidence, 144
laboratory diagnosis, 145
treatment, 146
Streptomycin, in bronchopulmonary disease, 237, 238
in infectious croup, 178
in nasopharyngeal infections, 163
in staphylococcal pneumonia and empyema, 225
in tuberculosis, 266
Streptonivicin in bronchopulmonary disease, 237, 238

Stridor, laryngeal, congenital, in newborn, roentgen diagnosis, 47
Subarachnoid hemorrhage in newborn, 57
Subdural hemorrhage in newborn, 56
  pathological findings, 57
Subependymal hemorrhage in newborn, 56
Suction in nasal obstruction, 159
Sulfonamides, in bronchopulmonary disease, 237, 238
  in nasopharyngeal infections, 165
  in streptococcal infection, 146
  sulfadiazine, in streptococcal infection, prophylactic, 150
  sulfisoxazole, in croup, 178, 179
Sus-Phrine in bronchial asthma, 299
Sweat test in fibrocystic disease of pancreas, 235

TEMPERATURE, environmental, effect on incidence of common cold, 106, 107
Teratomas, 83
Tetracycline(s), in bronchopulmonary disease, 237, 238
  in nasopharyngeal infections, 164
  in staphylococcal pneumonia and empyema, 225
Thiomycetin in whooping cough, 281
Thorax, abnormalities, 96
  bell-shaped, in newborn, 28, 29
  funnel chest, 96
  intrathoracic masses, congenital, in newborn, roentgen diagnosis, 49
  normal, in newborn, roentgen findings, 28
  retraction, in newborn, 23
  roentgen findings in infectious mononucleosis, 132
Throat, culture, in streptococcal infection, 145
  infections, herpangina, 115–20
    clinical manifestations, 118
    complications, 119
    course, 119
    differential diagnosis, 119
    epidemiology, 116
    etiology, 116
    prognosis, 119
    treatment, 119
    vs. pharyngoconjunctival fever, 125
Thymus, normal, in newborn, roentgen findings, 30
Thyroid gland, lingual, 79
Tissue respiration, 8
Tongue, cyst, thyroglossal, 79
  strawberry, in streptococcal infection, 142
Tonsillectomy in prophylaxis of common cold, 110
Trachea, abnormalities, 80–1
  foreign body in, vs. croup, 176
  normal, in newborn, roentgen findings, 31
Tracheocele, 81
Tracheo-esophageal fistula, 83–5
    roentgen diagnosis, 36
    without esophageal atresia, 84
    with esophageal atresia in newborn, 66
Tracheomalacia, 80
Tracheotomy in infectious croup, 179
Trachiectasis, 81
Tuberculin test, advantages, 261
    methods, 262
Tuberculosis, pulmonary, primary, control of, 261
      course, 257
      prognosis, 257
      specific vs. nonspecific therapy, 255–70
      treatment, 263
        drug dosages and schedules, 265
        nonspecific, 267
        specific, 266
  vaccination, BCG, 262, 263

VACCINES, in prophylaxis of common cold, 110
  pertussis, 278
Vasoconstrictors in nasopharyngeal infections, 158
Vincent's infection vs. streptococcal infection, 144
Viruses, Coxsackie, group A, infections with, 115–20. See also *Throat, infections, herpangina.*
Vocal cords, paralysis, in newborn, 67

WHOOPING cough, catarrhal stage, 272
    clinical manifestations, 272
    complications, 274
    course, 273
    diagnosis, 276
    differential diagnosis, 274
    incidence, 271
    paroxysmal stage, 272
    preparoxysmal stage, 272
    prevention, 278
      and treatment, 271–83
    resolution, 273
    treatment, 279